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CLINICAL COURSE AND TREATMENT OF SPRUE

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Job, chap. 30, verse 27: "My bowels boiled, and rested not; the days of affliction prevented me."

Job, chap. 32, verse 19: "Behold, my belly is as wine which hath no vent; it is ready to burst like new bottles."

Tropical sprue as a medical problem is confined to certain sharply delineated geographic areas. As a problem in pathologic physiology, however, the disease has been shown in recent years to be of considerable general importance and interest. The recent reviews of Castle, Rhoads, Lawson and Payne,[1] of Fairley[2] and of Reed[3] have all dealt at length with the history and symptomatology of tropical sprue. Consideration of these reports, however, reveals that a certain difference of opinion exists as to the most effective means of treating sprue and indeed as to the basic mechanism of the disease process. The patients reported on by Reed and by Fairley were treated both by dietary means and by the administration of liver extract, whereas those reported on by Castle and his associates were treated uniformly with liver extract alone, but they were followed for too short a time to allow accurate estimations of the effect of therapy.

A clinical study of thirty-three patients with sprue has been made in this hospital during the past four and a half years. Information is available concerning twenty-nine of these patients over periods varying from three months to four and a half years after they were discharged from the institution. The salient facts concerning these patients both during hospitalization and after their discharge are presented in this report.

From the Hospital of the Rockefeller Institute for Medical Research.

1. Castle, W. B.; Rhoads, C. P.; Lawson, H. A., and Payne, G. C.: Etiology and Treatment of Sprue, Arch. Int. Med. **56**:627 (Oct.) 1935.

2. Fairley, N. H.: Tropical Sprue with Special Reference to Intestinal Absorption, Brit. M. J. **1**:1176, 1936; Tr. Roy. Soc. Trop. Med. & Hyg. **30**:9, 1936.

3. Reed, A. C.: Sprue, a Clinical Summary, Am. J. Trop. Med. **16**:499, 1936.

MATERIAL

All except four of the thirty-three patients studied had resided in tropical or subtropical countries; eleven had lived in China, nine in Puerto Rico, four in Central or South America and one each in Cuba, Turkey, Algeria, Japan and the Philippine Islands. Twenty-five of the patients were females, and eight were males.

In this report the patients have been divided into three groups according to the presence or absence of certain symptoms and clinical findings at the time of the patients' admission to this hospital. All the patients gave histories which were characteristic of sprue, but in this report the histories are disregarded as far as the grouping is concerned. Group A includes those patients who presented the classic picture of severe sprue when first admitted to the hospital; all of them had diarrhea, gastro-intestinal distress and well marked anemia. Group B is made up of those patients who suffered from diarrhea and gastro-intestinal distress but showed no significant degree of anemia. Group C comprises those who presented neither diarrhea nor anemia when they came under observation but complained only of abdominal discomfort and distention.

Group A: Patients with Anemia and Diarrhea on Entry.—Ten patients presenting the classic picture of severe tropical sprue make up this group. Eight had resided in tropical or subtropical countries, but the other two had never been south of Florida or Texas, respectively. The clinical pictures presented by the last two patients differed in no respect from those seen in the others of the group.

Gastro-Intestinal Symptoms (Table 1): Recurrent disturbances of the gastro-intestinal tract had been present for periods varying from four to twenty years. The most prominent and the most distressing of these symptoms was diarrhea, which had occurred in all the patients. Vomiting had been a prominent feature at one time or another in six of the patients, while nausea was a complaint common to the entire group. Abdominal distention and discomfort had occurred in all.

At the time of the patient's admission to the hospital the stools varied in number from four to twenty per day and were in general voluminous and yellow, with a yeasty odor. In certain instances, however, they were watery and not to be distinguished from any other diarrheal stool. Besides the diarrhea these patients complained of abdominal discomfort associated with cramps, flatulence, distention, borborygmi and the eructation of gas.

Loss of Weight (Table 2): Nine of the patients had lost weight over periods of from one to sixteen years. The amount of weight lost varied from 13.6 to 53.6 Kg., and all nine patients were markedly emaciated when admitted. After treatment six patients gained weight rapidly, the weight of one patient being increased by 15 Kg. in less than six weeks.

Oral Symptoms (Table 3): Recurrent soreness of the tongue and mouth had been noticed by nine of these patients over periods varying from one to fifteen years. In most instances the onset of the oral symptoms took place some time after the onset of the gastro-intestinal symptoms. Two types of soreness of the mouth were reported. One type consisted of redness and burning of the tongue and the other of ulceration of the buccal and gingival mucous membrane, accompanied

TABLE 1.—*Gastro-Intestinal Symptoms*

			Before Entry into Hospital				At Entry	
Case	Patient	Sex	Vomiting	Flatulence	Diarrhea	Years Before Entry	Flatulence	Diarrhea
				Group A				
1	R. D.	F	+	+	+	7	+	+
2	M. F.	F	+	+	+	4	+	+
3	M. G.	F	+	+	+	18	+	+
4	B. M.	F	+	+	+	7	+	+
5	L. N.	F	+	+	+	20	+	+
6	G. M.	M	0	+	+	16	+	+
7	E. M.	F	+	+	+	9	+	+
8	C. O.	F	0	+	+	20	+	+
9	L. S.	F	0	+	+	15	+	+
10	R. S.	F	0	+	+	7	+	+
				Group B				
11	M. B.	F	+	+	+	4	+	+
12	R. B.	M	+	+	+	9	+	+
13	A. D.	F	0	+	+	2½	+	+
14	F. E.	F	0	+	+	1	+	+
15	M. L. F.	F	0	+	+	11	+	+
16	P. M.	M	0	+	+	8	+	+
17	M. P.	M	0	+	+	1½	+	+
18	E. R.	F	0	+	+	6	+	+
19	H. W.	M	0	+	+	1	+	+
				Group C				
20	R. C.	M	0	+	+	1	+	0
21	A. DeG.	F	0	+	+	3	+	0
22	R. F.	F	0	+	+	15	+	0
23	F. H.	F	+	+	+	24	+	0
24	L. H.	F	0	+	+	2	+	0
25	P. K.	M	0	+	+	13	+	0
26	G. L.	M	0	+	+	3	0	0
27	E. P.	F	+	+	+	5	0	0
28	R. P.	F	0	+	+	7	0	0
29	M. P.	F	+	+	+	12	+	0
30	E. P.	F	+	+	+	6	+	0
31	B. R.	F	+	+	+	25	+	0
32	E. S.	F	0	+	+	8	+	0
33	A. W.	F	0	+	+	1	+	0

at times with pain and burning of the whole oral cavity. Salivation was frequently a distressing symptom.

At the time of admission to the hospital nine of the patients had visible oral lesions, which consisted of (1) atrophy of the lingual papillae, (2) redness of the tongue and oral mucosa and (3) vesicular and ulcerated lesions of the tongue and mucous membrane. These various types of oral lesions occurred singly or in any combination. Six patients in this group had atrophic glossitis; one of these had aphthous lesions of the tongue, and another had similar lesions of the oral mucosa.

Redness of the tongue was present in three patients; one of these showed also reddening of the oral mucosa, and two of them had aphthae as well.

Gastric Analysis (Table 4): A standard method of gastric analysis was employed, consisting of the withdrawal of four specimens of gastric juice. The first specimen was taken from the stomach during fasting, the second twenty minutes after an alcohol test meal, the third forty minutes after the alcohol meal and the fourth twenty minutes after the

TABLE 2.—*Loss of Weight*

Case	Loss of Weight, Kg.	Duration of Symptoms	Weight at Entry, Kg.	Weight at Discharge, Kg.
		Group A		
1	+	7 years	41.5	54.9
2	53.6	4 years	42.0	57.0
3	13.6	5 years	45.2	42.0
4	+	7 years	55.9	52.4
5	43.2	15 years	52.5	55.7
6	+	16 years	45.9	48.6
7	22.4	1 year	31.4	42.4
8	0	.....	68.7	68.0
9	21.8	3 years	35.4	37.3
10	17.3	7 years	43.7	43.1
		Group B		
11	9.1	4 years	44.7	45.7
12*	+	9 years	63.8	63.6
			69.8	71.4
13	18.2	2½ years	58.2	56.8
14	+	11 months	48.4	49.0
15	0	.....	55.0	56.7
16	0	.....	70.6	70.2
17	+	14 months	50.1	49.9
18	0	.....	65.7	67.4
19	+	1 month	56.8	57.6
		Group C		
20	0	.....	76.2	....
21	+	3 years	51.9	53.0
22	0	.....	60.4	61.5
23	4.6	2 years	56.4	56.7
24	12.3	2 years	49.0	50.1
25	13.6	3 years	59.7	59.8
26	13.6	3 years	93.2	89.2
27	0	.....	73.2	....
28	+	14 months	50.1	49.9
29	0	.....	61.5	62.4
30	+	6 years	....	....
31	9.1	10 years	41.9	42.7
32	0	.....	52.2	....
33	18.2	2 years	....	....

* The patient was admitted to the hospital on two different occasions.

intramuscular injection of 0.5 mg. of histamine. In table 4 the volume of gastric juice obtained and the amount of free hydrochloric acid present in each specimen are tabulated.

Failure of the stomach to secrete free hydrochloric acid after the injection of histamine was observed in only one patient (case 6). In four other patients free hydrochloric acid was absent until after the injection of histamine. In only one patient (case 10) was the amount of free hydrochloric acid greater than 30, and in most instances the volume of gastric juice obtained was small.

Blood Picture (Table 5): Nine of the patients gave a history of having had anemia before admission to the hospital. In one instance the anemia had been present for ten years before entry, but in the other cases it was of more recent origin. The exact nature of the type of anemia which was present before admission was unknown except for

TABLE 3.—*Oral Sympotms*

Case	Sore Tongue	Sore Mucous Membrane	Period of Observation Before Entry	Observed at Entry
			Group A	
1	+	+	7 years	Atrophy of papillae
2	+	+	4 years	Atrophy of papillae
3	+	+	5 years	Atrophy of papillae
4	+	+	5 years	Atrophy of papillae; aphthae of mucous membrane
5	+	..	15 years	Aphthae of tongue; atrophy of papillae
6	+	+	2 years	Red, smooth tongue; aphthae, red mucosa
7	+	+	1 year	Red, smooth tongue
8	+	+	5 years	Red tongue; aphthae of mucosa
9	0	0	.....	
10	+	+	7 years	Atrophy of papillae
			Group B	
11	+	+	3½ years	Aphthae of mucosa
12	+	+	9 years	
13	+	+	1½ years	Atrophy of papillae; aphthae of mucous membranes
14	+	+	11 months	Red tongue
15	+	+	8 years	Aphthae of mucous membrane
16	+	+	1½ years	
17	+	+	4 months	Red, smooth tongue; aphthae of tongue and mucosa
18	+	+	6 years	Atrophy of papillae; aphthae of mucous membrane
19	+	+	6 months	Red tongue; atrophy of papillae
			Group C	
20	0	0	.....	
21	+	+	3 years	
22	0	+	10 years	Tongue red along edges
23	+	+	2 years	Tongue red along edges; atrophy of papillae
24	0	+	1 year	
25	+	0	13 years	Slight atrophy of papillae
26	+	+	4 years	Slight atrophy of papillae; tongue red at tip
27	0	+	1 year	Slight atrophy of papillae
28	+	+	7 years	
29	+	+	6 months	Aphthae of mucosa; tongue smooth
30	+	+	6 years	
31	0	+	3 years	
32	+	+	3 years	Redness and aphthae of tongue and mucous membrane
33	+	0	.....	

one patient (case 7), in whom microcytic hypochromic anemia had been noted. A red blood cell count of less than 3,500,000 per cubic millimeter was arbitrarily selected as indicative of distinct anemia, since the frequent macrocytosis warranted the employment of erythrocyte counts rather than hemoglobin values as a criterion.

At the time of admission to the hospital all of these ten patients had red blood cell counts of less than 3,500,000, and the erythrocyte levels of two were below 1,000,000. The hemoglobin values were relatively high, giving all the patients, except in cases 6 and 9, a definitely

macrocytic hyperchromic blood picture. The color index and the mean corpuscular volume were well above the normal range and in many instances were at levels as high as those seen in pernicious anemia. In cases 6 and 9 the anemia was of a normocytic type.

As in pernicious anemia, the number of white blood cells was decreased, in six cases below 5,000. In only one was the count more than 6,000.

TABLE 4.—*Gastric Analyses* *

Case	Volume, Cc.				Free Hydrochloric Acid			
	I	II	III	IV	I	II	III	IV
Group A								
1	17	15	15	28	0	0	0	17
3	30	20	15	25	0	0	20	79
4	35	20	12	19	0	4	10	13
5	25	21	12	16	0	0	0	7
6	20	30	15	30	0	0	0	0
7	16	42	8	24	0	0	0	25
8	38	62	18	..	0	0	24	11
9	40	25	15	30	0	0	0	36
10	86	35	30	..	6	62	122	..
Group average	33.0	30.0	15.5	24.6	0.7	7.3	19.5	23.5
Group B								
12	..	..	..	..	20	36	..	96
13	12	11	9	..	0	6	8	..
14	26	15	25	..	0	9	31	..
15	12	20	24	13	0	0	0	0
16	..	..	..	..	11	..	..	22
18	15	..	22	13	0	..	10	16
19	30	35	30	20	14	67	91	99
Group average	19.0	20.3	22.0	15.3	6.4	23.6	28.0	46.6
Group C								
20	23	15	10	20	0	0	0	0
21	30	25	20	35	0	23	37	70
22	20	10	15	30	5	9	20	38
23	22	20	15	..	0	0	12	..
24	10	12	15	30	0	8	14	31
25	30	75	25	40	0	30	50	97
26	..	..	..	..	0	3	58	..
27	14	15	10	25	0	0	14	32
28	66	42	30	..	25	25	56	..
29	40	9	15	..	6	27	30	..
30	55	40	15	60	0	24	20	53
31	30	10	12	16	2	8	14	20
32	30	12	32	40	0	0	0	0
33	10	10	24	40	10	18	24	40
Group average	29.2	22.5	18.3	33.6	3.4	12.5	24.9	38.1
Series average	29.0	24.8	18.0	27.7	3.3	12.8	23.8	30.5

* I represents data for specimen taken during fasting; II, specimen taken twenty minutes after an alcohol test meal; III, specimen taken forty minutes after test meal; IV, specimen taken twenty minutes after injection of histamine. The volumes under specimen I do not always represent actual volumes during fasting, as some of the patients were allowed to sip water while swallowing the tube.

By comparing the red blood cell count at the time of the patient's discharge with that on entry, the effect of antisprue therapy on the hematopoietic system is evident. More detailed studies of the blood are shown in the two accompanying charts (figs. 1 and 2; cases 4 and 5, respectively). In each of these patients a rise in the reticulocyte count occurred and was followed by a remission.

The two following abstracts of cases are given to illustrate the type of patient included in this group:

CASE 4.—B. M., a 37 year old American woman, entered the hospital complaining of attacks of diarrhea for seven years. She had resided in Cuba for twelve years. Seven years before entering the hospital she began to have attacks

TABLE 5.—*Data on the Blood*

		Values at Entry					Values at Discharge				
Case	Anemia Observed Before Entry	Erythrocytes, Millions per Cu. Mm.	Hemoglobin, Percentage	White Blood Cells per Cu. Mm.	Mean Corpuscular Volume, Cu. Microns	Color Index	Erythrocytes, Millions per Cu. Mm.	Hemoglobin, Percentage	White Blood Cells per Cu. Mm.	Mean Corpuscular Volume, Cu. Microns	Color Index
					Group A						
1	1 yr.	0.82	22	2,100	131	1.34	4.17	76	5,200	92	0.92
2	1 yr.	1.13	30	3,250	115	1.33	3.45	78	6,750	102	1.12
3	+	0.90	30	1,400	121	1.67	3.67	77	3,800	101	1.05
4	5 yr.	2.05	67	2,050	135	1.63	3.98	92	7,250	100	1.16
5	1½ yr.	1.38	35	1,150	102	1.27	3.04	67	6,650	97	1.12
6	+	3.10	59	9,600	91	0.95	3.90	80	6,700	101	1.03
7	10 yr.	3.30	70	5,100	...	1.06	4.90	94	.....	...	0.96
8	5 yr.	2.96	79	5,400	138	1.34	3.85	82	7,700	100	1.06
9	3 mo.	3.15	53	4,650	78	0.84	3.47	62	5,300	79	0.90
10	0	3.12	81	5,500	118	1.30	....	..	.....	...	....
Group average		2.19	53	4,020	114	1.27	3.83	79	6,170	96.5	1.04
					Group B						
11	4 yr.	4.61	97	12,850	90	1.05	4.97	100	12,250	86	1.05
12	5 yr.	3.59	92	5,150	113	1.28	4.68	94	7,950	90	1.01
13	2 yr.	3.67	87	7,700	108	1.19	....	..	.....	...	....
14	11 mo.	4.69	77	6,100	74	0.83	5.36	77	8,900	70	0.72
15	0	4.40	95	.....	111	1.08	....	..	.....	...	....
16	6 mo.	4.64	105	5,900	95	1.14	4.37	105	6,350	102	1.20
17	2 mo.	3.52	58	7,150	...	0.83	3.87	59	9,900	75	0.77
18	5 yr.	4.02	83	7,000	94	1.04	....	..	.....	...	....
19	0	4.47	86	8,300	91	0.98	4.54	94	.....	102	1.04
Group average		4.18	87	7,520	97	1.05					
					Group C						
20	0	4.42	99	4,100	...	1.12	....	..	.....	...	....
21	8 mo.	3.57	97	4,150	...	1.36	4.06	94	5,250	108	1.17
22	10 yr.	5.05	99	4,000	84	0.98	4.62	90	4,300	86	0.98
23	+	3.48	90	7,550	103	1.30	3.39	92	5,400	115	1.36
24	0	4.08	91	6,500	99	1.12	4.13	84	7,950	92	1.12
25	0	3.87	96	4,150	106	1.24	....	..	.....	...	....
26	3 mo.	4.18	106	4,300	110	1.27	....	..	.....	...	....
27	0	3.94	100	2,450	72	1.27	....	..	.....	...	....
28	0	3.94	90	9,350	...	1.14	....	..	.....	...	....
29	0	4.57	96	7,400	89	1.05	....	..	.....	...	....
30	6 yr.	3.72	89	6,350	101	1.20	....	..	.....	...	....
31	0	3.96	83	7,600	82	1.05	....	..	.....	...	....
32	3 yr.	3.60	91	8,600	115	1.27	3.85	96	7,000	104	1.25
33	0	3.51	90	10,150	102	1.28	3.57	83	8,600	...	....
Group average		3.99	94	6,190	97	1.19					

of diarrhea accompanied with nausea, vomiting and abdominal cramps. Two years after the onset of these attacks the patient moved to a temperate climate and was free from symptoms for six months. At the end of that time the diarrhea returned, with soreness of the tongue and mouth. Anemia of severe degree was present. Liver extract was given by mouth; the diarrhea ceased, and the red blood cell count rose to 4,000,000 per cubic millimeter. The patient was well for one year; then the diarrhea and soreness of the mouth recurred but were alleviated by the use of a diet of meat and eggs. The anemia was not relieved by this diet, and two transfusions were given. She was well until one year before admission to the

hospital, when the diarrhea recurred and the high protein diet afforded no relief. About two months before she entered the hospital weakness and pallor appeared and were not relieved by orally administered liver extract.

Physical Examination.—The patient was fairly well nourished but was pale. The tip and dorsum of the tongue showed atrophy of the papillae. There was a small yellow ulcer on the mucosa of the upper lip. The abdomen was distended and tympanitic.

Laboratory Examination.—Gastric analysis showed free hydrochloric acid in all specimens except the one taken during fasting. There were 2,000,000 erythrocytes per cubic millimeter, 66 per cent hemoglobin, a color index of 1.65 and a mean corpuscular volume of 135 cubic microns.

Course.—During the first three days the patient had from ten to fifteen bowel movements a day. She was then given daily intramuscular injections of 10 cc.

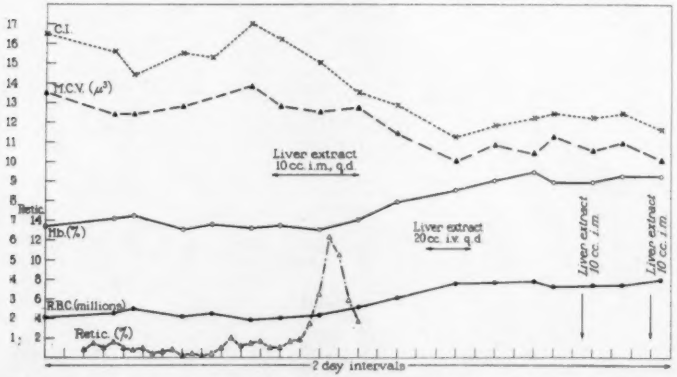

Fig. 1 (case 4).—Chart of the changes in the blood following the parenteral administration of liver extract. In figures 1 and 2 the values for the color index (*C. I.*) have been multiplied by 10; the values for the mean corpuscular volume (*M. C. V.*) in cubic microns have been divided by 10; the percentage values for hemoglobin (*Hb.*) have been divided by 10, and the values for erythrocytes (*R. B. C.*) have been divided by 1,000,000.

of liver extract,[4] an amount derived from 50 Gm. of whole liver. On the tenth day the reticulocyte count reached a peak of 12.8 per cent (fig. 1). This was followed by an improvement in the blood values, and the patient was discharged from the hospital two months after entry, with an erythrocyte count of 3,980,000 and a hemoglobin value of 92 per cent. After discharge she received 10 cc. of liver extract every two weeks by intramuscular injection, and on this regimen she was symptom free for nearly a year.

Nine months after discharge the patient went to Florida and discontinued the injections of liver extract. Two months later diarrhea recurred, and the patient lost her appetite and grew progressively weaker. From that time until her return to the hospital, five months later, attacks of diarrhea, soreness of the mouth and tongue, loss of weight and weakness became progressively worse. When readmitted she was having from fifteen to twenty evacuations daily.

4 Liver extract-Lilly (N. N. R.) was used.

Physical Examination.—The patient was emaciated. The tongue was red at the tip and along the margins. The buccal mucosa was injected, and there were several aphthous lesions. The abdomen was moderately distended, and peristaltic rushes were audible.

Laboratory Examinations.—The results showed: erythrocytes, 2,230,000; hemoglobin, 62 per cent; color index, 1.39, and mean corpuscular volume, 115 cubic microns.

Course.—The patient was given 10 cc. of liver extract by intramuscular injection daily for five days. Soreness of the tongue disappeared after the first injection, and the aphthous ulcers healed rapidly. Diarrhea ceased after the third injection. The number of injections of liver extract was decreased to two a week. In ten days the patient gained 2 Kg. in weight. One month later the erythrocyte count was 3,350,000, and the hemoglobin value was 85 per cent. Injections of 10 cc. of liver extract intramuscularly have been continued twice each week, and with this therapy the patient has remained essentially symptom free.

CASE 5.—L. N., an American woman aged 45 who had resided in China for twenty-one years, had suffered from sprue for fifteen years. The presenting symptoms were stomatitis, glossitis, proctitis and diarrhea. Nine years before her entry into the hospital a remission had followed the use of a diet with a high protein, a low fat and a low carbohydrate content. For three years before her admission to the hospital nausea, vomiting and diarrhea, with marked loss of weight, had been present. For six months the patient had been in bed, able to retain only milk and toast. Twice a week during the three months immediately preceding her admission to the hospital she had received an intramuscular injection of 2 cc. of liver extract, an amount derived from 10 Gm. of whole liver.

Physical Examination.—The patient was markedly emaciated. Pallor and faint yellowness of the skin and mucous membranes were noted. The tongue showed atrophy of the papillae. There was edema of the legs.

Laboratory Examination.—The results showed: erythrocytes, 1,380,000; hemoglobin, 35 per cent; white blood cells, 1,150; mean corpuscular volume, 102 cubic microns; color index, 1.27. Gastric analysis showed free hydrochloric acid only after the injection of histamine.

Course.—The patient was given 20 cc. of liver extract [5] intravenously each day during her stay in the hospital. On the seventh day of treatment the reticulocyte value rose to 43.2 per cent. This reticulocyte response was followed by an increase in the erythrocyte count and in the hemoglobin value (fig. 2). Diarrhea ceased soon after the injections of liver were begun. The patient's appetite improved, and she was discharged three weeks after entry, with an erythrocyte count of 3,040,000 and a hemoglobin value of 67 per cent.

After discharge from the hospital the patient moved to Alabama. She has received an intramuscular injection of 10 cc. of liver extract every two weeks, and with this therapy she has remained free from symptoms for the past two and a half years.

Summary: These ten patients with severe sprue have been grouped together because of the fact that anemia as well as gastro-intestinal disturbance was present at the time of admission to the hospital. The histories of two patients in this group are presented. Case 4 demon-

5. Liver extract-Parke, Davis & Co. (N. N. R.) was used.

strates the therapeutic failure of orally administered liver extract, as well as the necessity of continued therapy. Case 5 is presented because it is typical of severe sprue and illustrates the dramatic results that can be obtained by intensive therapy with parenterally administered liver extract without change of diet.

Group B: Patients With Diarrhea but Without Anemia.—This group is made up of nine patients who had distention and diarrhea but no anemia at the time of admission to the hospital. The lack of disturbance of hematopoiesis separates these patients from those just described. Seven members of this group had resided in tropical or

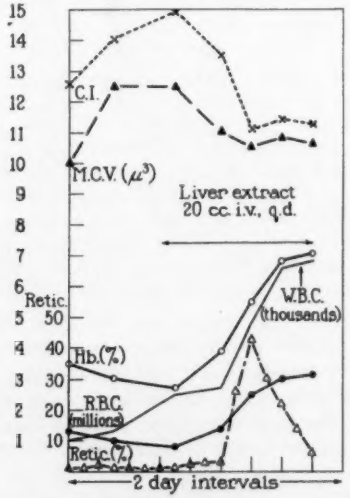

Fig. 2 (case 5).—Chart of the changes in the blood following the parenteral administration of liver extract.[5]

subtropical countries, whereas two had not been out of the temperate zone.

Gastro-Intestinal Symptoms (Table 1): Recurrent attacks of distention and diarrhea had occurred in every instance over periods varying from one to nine years. The gastro-intestinal symptoms did not differ from those of the patients in group A, except that nausea and vomiting had been less frequent and the attacks of diarrhea had not extended over so long a period.

At the time of admission to the hospital all these patients had diarrhea. The stools were on the whole not so numerous as those of the patients of group A but were of similar type.

Loss of Weight (Table 2): Six of the nine patients had lost weight over periods of from one month to nine years, but the average loss was not as great as in the preceding group, and the patients were not so emaciated. Since the period of hospitalization was relatively short, the gain in weight was correspondingly less striking in this group.

Oral Symptoms (Table 3): The oral symptoms of these patients were identical with those of the patients in group A. All of these patients had noticed soreness of the tongue or of the mouth over periods varying from four months to nine years. In most instances the oral symptoms first developed after the onset of the diarrheal attacks.

The same types of oral lesions were observed as have been described for the patients with more severe involvement. Two of these patients had no oral changes when they were admitted to the hospital, although they both gave a history of soreness of the mouth. Four patients had aphthous lesions of the oral mucosa, and two of these showed also atrophic glossitis. Three other patients were suffering from acute glossitis, with redness of the tongue; of these, one had atrophy of the papillae as well, and another had aphthous ulcers of the buccal mucosa.

Gastric Analysis (Table 4): Gastric analyses were carried out for seven patients of this group. In only one patient (case 15) was no free hydrochloric acid found in the gastric juice after the injection of histamine. The other six patients showed free hydrochloric acid either in the specimen taken during fasting or after the alcohol test meal. The quantities of gastric juice obtained were small.

Blood Picture (Table 5): Some of the nine patients gave a history of having suffered from anemia at some time during the course of their illness. However, at the time of admission to the hospital all the patients had red blood cell counts above 3,500,000. One patient (case 17) showed a hemoglobin value of 58 per cent; nevertheless, he is included in this group, since the erythrocytes numbered 3,520,000. Three of the patients had erythrocyte counts between 3,500,000 and 4,000,000; three had counts between 4,000,000 and 4,500,000, and three had counts between 4,500,000 and 5,000,000. In three instances the mean corpuscular volume and the color index were above the normal range, giving these three patients (cases 12, 13 and 15) a slightly macrocytic hyperchromic blood picture. In all the remaining cases the blood was normocytic.

CASE 12.—R. B., a white man aged 56, had suffered from sprue for nine years before admission to the hospital. He had resided in Puerto Rico for five years when diarrhea first developed. This attack was characterized by large foamy stools and was accompanied with nausea and vomiting. Soon after the onset of the gastro-intestinal symptoms his tongue became sore, and salivation increased. During the next two years diarrhea, consisting of two or three spruelike stools, persisted, and the tongue was sore from time to time. Four years after the onset

of symptoms the patient returned to the United States. At that time he had lost about 15 pounds (7 Kg.) in weight; diarrhea and soreness of the tongue and mouth were still present. The administration of liver by mouth was followed by striking improvement. When he discontinued liver therapy a year later, diarrhea again developed, and he began to lose weight. For fifteen months he was given daily intramuscular injections of 3 cc. of liver extract.[4] On this regimen he felt well but finally tired of the injections and discontinued them. He was then given three vials of liver extract [4] a day by mouth with the result that diarrhea and the loss of weight soon recurred, along with increasing fatigue. He was given 2 cc. of liver extract by intravenous injection once a week, with no improvement in his symptoms. There was no response to a strict dietary regimen for sprue.

Physical Examination.—The patient was well developed and fairly well nourished but appeared to be chronically ill. There were raised, rough, granular patches of skin over the elbows and knees. The tongue and mouth showed no abnormality.

Laboratory Examinations.—Gastric analysis showed free hydrochloric acid in all specimens. Study of the blood showed: erythrocytes, 3,590,000; hemoglobin, 92 per cent; leukocytes, 5,150; color index, 1.28, and mean corpuscular volume, 113 cubic microns.

Course in Hospital.—The patient was given a diet for sprue and daily intravenous injections of 20 cc. of liver extract (the amount derived from 50 Gm. of whole liver). Dramatic relief from symptoms and complete amelioration of the gastro-intestinal disturbances resulted. The patient was discharged three and a half weeks after admission to the hospital, with instructions to take 20 cc. of liver extract by intravenous injection once a week.

Subsequent Course.—After leaving the hospital the patient received 20 cc. of liver extract intravenously every ten days. After each injection the stools were formed for three days, semiformed for three days and loose and foamy for the last four days of the interval between injections. Marked flatulence accompanied the diarrhea, but no recurrence of the stomatitis or anemia developed. In spite of the gastro-intestinal disturbances the patient gained 6.2 Kg. in the six months following his discharge from the hospital. He was then readmitted and treated with daily intravenous injections of 20 cc. of liver extract for eleven days. On the third day of this course of therapy the stools became formed and remained so during the patient's stay in the hospital. He was again discharged as symptom free and received two intravenous injections of liver extract a week after that. On this regimen he has remained symptomatically well for nine months.

CASE 15.—M. L. F., a 42 year old American woman who had resided for twelve years in southern China, had suffered from sprue for eleven years. The first attack of diarrhea occurred eleven years before her entry into the hospital and was not accompanied with fever, nausea or vomiting. Attacks of diarrhea recurred frequently during the next three years and were accompanied with soreness of the tongue and mouth. For the next five years the patient was symptom free. Three years before her entry into the hospital diarrhea with soreness of the tongue and mouth returned. After one year she was given a diet for sprue, consisting of liver, meat, fresh vegetables and fruits; on this diet she was symptom free for six months, after which her symptoms returned. For one year before her entry into the hospital the diarrhea was so severe that she was forced to give up her work and return to this country.

Physical Examination.—The patient was fairly well nourished. The tongue showed no atrophy of the papillae, but there were numerous small yellow ulcerations of the buccal mucosa. The abdomen was moderately distended and tympanitic. Peristalsis was audible.

Laboratory Examination.—Gastric analysis showed no free hydrochloric acid, even after the injection of histamine. Study of the blood showed: red blood cells, 4,400,000; hemoglobin, 95 per cent; white blood cells, 5,600; mean corpuscular volume, 111 cubic microns, and color index, 1.08.

Course.—The patient was given a diet with a high protein, a low fat and a low carbohydrate content. Five cubic centimeters of liver extract was given intramuscularly daily for five days and then 20 cc. by intravenous injection daily for eight days. With this therapy the diarrhea and flatulence ceased, and the oral lesions disappeared. The patient was discharged six weeks after entry.

After discharge the patient received intramuscular injections of 10 cc. of liver extract twice a week for one month. The interval between injections was then lengthened, depending on how long the patient remained symptom free. Nine months after discharge from the hospital the patient returned to China. Since then she has received 10 cc. of liver extract by intramuscular injection every two or three weeks and has remained entirely free from symptoms.

Summary: This group consists of nine patients who had sprue with diarrhea but without anemia. Their complaints at the time of entry were chiefly of gastro-intestinal disorders. Two typical cases of this group are presented, both of which illustrate the amelioration of intestinal dysfunction which may be obtained by the parenteral injection of liver extract, although dietary therapy has been ineffective.

Group C: Patients Without Anemia or Diarrhea.—This group includes fourteen patients who had no diarrhea or anemia at the time of admission to the hospital. All had resided in tropical or subtropical countries, and all presented symptoms which warranted the diagnosis of sprue.

Gastro-Intestinal Symptoms (Table 1): Before entry into the hospital all these patients had had repeated attacks of flatulence and diarrhea over periods varying from one to twenty-five years. These attacks did not differ from those of the patients in the preceding groups. Five patients complained of nausea and vomiting as a frequent symptom. All the patients in the group had had voluminous, frothy, yellow, foul stools at one time. The ingestion of fatty or starchy foods had aggravated their symptoms.

On admission to the hospital these patients had no diarrhea. All except three of them had severe abdominal discomfort marked by abdominal cramps, audible peristalsis, rumbling of gas and frequent expulsion of gas both by mouth and by rectum. The stools were often soft or semiformed, but many had formed stools which were of normal appearance.

Loss of Weight (Table 2): Loss of weight had taken place in ten patients over periods varying from fourteen months to ten years. For the patients who had kept accurate figures for the amount of weight lost the values ranged from 4.6 to 18.2 Kg. At entry the patients were not so emaciated as those of group A or group B.

Oral Symptoms (Table 3): The oral symptoms of these patients were similar to those of the patients in the preceding groups. Before admission thirteen of the patients had suffered from soreness of the mouth at irregular intervals over periods varying from six months to thirteen years. In seven cases soreness of both the tongue and the oral mucosa had occurred, while two patients complained of soreness of the tongue alone and four patients of soreness limited to the oral mucous membranes.

At the time of admission to the hospital seven patients presented oral lesions. Five had atrophic glossitis; of these, two showed reddening of the tongue, and one had aphthous ulcers on the buccal mucosa. Two other patients had no papillary atrophy but did have redness of the tongue; one of them had aphthous lesions of both the tongue and the oral mucosa.

Gastric Analysis (Table 4): Gastric analyses were made for all the patients of this group. In two patients (cases 20 and 32) no free hydrochloric acid was found in the gastric juice even after the injection of histamine. In two patients (cases 23 and 27) free hydrochloric acid first appeared in the specimen taken forty minutes after the administration of the alcohol test meal. In most instances the volume of gastric juice and the content of free hydrochloric acid were approximately normal. The results of the gastric analyses for these patients approached the normal more closely than did those for the patients in the other two groups.

Blood Picture (Table 5): Anemia had occurred in six of these patients at periods varying from three months to ten years before entry, but at the time of admission to the hospital it was present in none. The red blood cell counts of eight patients were between 3,500,000 and 4,000,000; the other six had counts of over 4,000,000. The hemoglobin levels for seven of the patients were relatively high in proportion to the erythrocyte counts, and the values for the mean corpuscular volume and the color index were above the normal range. Thus, these seven patients showed a moderately macrocytic hyperchromic blood picture, even though they did not have anemia. In three cases the mean corpuscular volume was not determined, but the color index was high. The remaining four patients in the group had a normocytic type of blood picture.

CASE 29.—M. P., a 57 year old American woman, was admitted to the hospital with complaints of soreness of the mouth and abdominal discomfort. For thirty-

two years prior to entry she had resided in Japan. She suffered her first attack of diarrhea, accompanied with nausea and vomiting, twelve years before admission to the hospital. She recovered from this episode and remained well until six years later, when abdominal discomfort, flatulence, diarrhea and soreness of the mouth developed. These symptoms persisted irregularly until one year before her entry into the hospital, when she had a severe attack of diarrhea. This symptom then disappeared, but the soreness of the mouth and flatulence persisted.

Physical Examination.—The patient was well developed and well nourished. Two small yellow punched-out ulcers were present on the mucous membrane of the lower lip. The tongue showed atrophy of the papillae well up over the dorsum. The remainder of the examination revealed essentially normal results.

Laboratory Examinations.—Gastric analysis revealed free hydrochloric acid in all specimens. Examination of the blood gave the following results: erythrocytes, 4,570,000; hemoglobin, 96 per cent; color index, 1.05; mean corpuscular volume, 89 cubic microns, and leukocytes, 7,400.

Course.—The patient had no diarrhea on entry but had marked flatulence and abdominal discomfort. She was given a diet for sprue and intramuscular injections of 10 cc. of liver extract daily for eight days. After this treatment the symptoms were markedly abated. The ulceration of the mouth disappeared, and the tongue was no longer sore. Abdominal discomfort, though still present, was much less marked at the time of the patient's discharge from the hospital. Thereafter she received two injections of liver extract a week for one month, then one injection a week for four weeks and finally one injection every two weeks. With this course of therapy she has become practically symptom free.

Case 32.—E. S., an American woman of 37 who had resided in Egypt and northern Africa for seven years, suffered her first attack of diarrhea six years before entry into the hospital. Five or six afebrile attacks characterized by from eight to ten loose to watery stools a day occurred during the first year of her illness. Two years later soreness of the tongue and mouth developed, diarrhea recurred frequently but was not so severe and the stools showed spruelike characteristics. Three years before entry liver extract was given by mouth, with improvement. One year later the patient was found to have microcytic anemia and was again given liver extract as well as iron by mouth. After this therapy the diarrhea ceased and had not recurred when the patient was seen in this clinic. At that time she complained chiefly of abdominal discomfort and flatulence. She was given a yeast autolysate [6] for two months. At the end of this period stomatitis and glossitis developed. The abdominal discomfort was still present, and she was admitted to the hospital.

Physical Examination.—The patient was well developed and well nourished. The only abnormalities noted were several aphthous ulcers on the buccal mucosa, with injection and redness of the entire oral mucous membrane. The tongue was red, raw and obviously sore.

Laboratory Examinations.—Gastric analysis showed no free hydrochloric acid even after the injection of histamine. Studies of the blood showed: erythrocytes, 3,600,000; hemoglobin, 91 per cent; color index, 1.27, and mean corpuscular volume, 115 cubic microns.

Course.—The patient was given 10 cc. of liver extract by intramuscular injection daily for four days. The glossitis, stomatitis and flatulence disappeared. Since discharge she has remained symptom free for ten months while taking a single intramuscular injection of 10 cc. of liver extract once every two weeks.

6. The preparation used was vegex.

Summary: This group consists of fourteen patients who gave a history of repeated attacks of diarrhea. All except one had had soreness of the mouth. None of them had diarrhea on admission to the hospital, but eleven had symptoms referable to the gastro-intestinal tract. This is a group of patients with "incomplete sprue," that is, patients observed between attacks of the disease. Two typical cases are presented, both

TABLE 6.—*Roentgen Studies of Small Intestine*

Case	Variation in Caliber		Changes of Mucosal Pattern		Segmentation
	Jejunum	Ileum	Jejunum	Ileum	
Group A					
1	+	+	+	+	+
3	..	+	+	+	..
4	+	+	+	+	+
5	+	+	+	+	+
6	+	+	+	+	+
7	+	+	+	+	+
8	+	+	+	+	+
9	+	+	+	..	+
10	..	+	+	+	+
Grand total (9 cases)	7	9	9	8	8
Group B					
11	..	+	+	..	+
12	..	+	..	+	+
13	..	+	+	+	..
14	+	+	+	+	+
15	+	+	+	..	+
16	..	+	+	+	+
17	..	..	..	..	+
18	..	+	..	..	+
19	..	+	..	+	+
Grand total (9 cases)	2	8	5	5	8
Group C					
20	+	+	+	..	+
21	..	+	+	..	..
22	+	+	+	..	+
25	..	+	..	+	..
26	+	+	+	+	+
27	..	+	..	..	+
28	..	+	..	+	..
29	+	..	+	..	..
30	..	+	..	+	+
32	..	+	..	+	+
33	..	+	..	..	+
Grand total (11 cases)	4	10	5	5	7
Series total (29 cases)	13	27	19	18	23

of which demonstrate the effect of liver extract on the minor gastro-intestinal symptoms.

ROENTGENOGRAPHIC PICTURE (TABLE 6)

Morphologic alterations in the small intestines of patients with sprue, as demonstrated by roentgenograms, have been described in a previous paper.[7]

7. Mackie, T. T.; Miller, D. K., and Rhoads, C. P.: Sprue: Roentgenologic Changes in the Small Intestine, Am. J. Trop. Med. **15**:571, 1935.

Furthermore, a return toward normal form and function has been shown by roentgenographic means to accompany the cessation of symptoms following the injection of liver extract.[8] The chief morphologic alterations have been summarized as follows: (1) a variation in the caliber of the intestinal segments; (2) a distortion of the mucosal pattern, usually of the jejunum but often of the duodenum and ileum as well, and (3) a segmental distribution of the barium, which is probably produced by abnormal motility of portions of the small intestine.

Among these alterations the variation in the caliber of the intestinal loops and the distortion of the mucosal pattern are the most characteristic changes in sprue. It is not assumed that these changes are pathognomonic of the disease; they are merely presented as observations which were made during the study of a large group of patients with sprue. Snell and Camp[9] have reported similar roentgenographic changes in cases of idiopathic steatorrhea. Recently Ravdin, Pendergrass and their associates[10] have studied the effect of various types of food on the roentgenographic pattern of the small intestine in normal persons. As these authors pointed out, it is of interest that after an olive oil meal the intestine shows changes much like those seen in patients with various forms of steatorrhea. Since poor fat absorption is a characteristic of sprue, it is possible that some of the changes observed in the pattern of the small intestine of patients with sprue are associated with the presence of an abnormal amount of fat in the bowel. Few adequate roentgenographic studies of the small intestine in disease states have been carried out; it is therefore difficult to compare the findings in sprue with those present in other intestinal disorders.

The method of roentgen examination used in this study was that previously described;[11] in the more recent studies the amount of barium sulfate used was reduced from 4 to 2 ounces (125 to 62 Gm.) at the suggestion of Dr. Golden, of the College of Physicians and Surgeons

8. Miller, D. K., and Rhoads, C. P.: The Effect of Liver Extract on the Small Intestine of Patients with Sprue, Am. J. M. Sc. **191**:453, 1936.

9. Snell, A. M., and Camp, J. D.: Chronic Idiopathic Steatorrhea: Roentgenologic Observations, Arch. Int. Med. **53**:615 (April) 1934; Proc. Staff Meet., Mayo Clin. **10**:177, 1935.

10. Ravdin, I. S.; Pendergrass, E. P.; Johnston, C. G., and Hodes, P. J.: The Effect of Foodstuffs on the Emptying of the Normal and Operated Stomach and the Small Intestinal Pattern, Am. J. Roentgenol. **35**:306, 1936. Pendergrass, E. P.; Ravdin, I. S.; Johnston, C. G., and Hodes, P. J.: Studies of the Small Intestine: II. The Effect of Foods and Various Pathologic States on the Gastric Emptying and the Small Intestinal Pattern, Radiology **26**:651, 1936.

11. Mackie, T. T., and Pound, R. E.: Changes in the Gastro-Intestinal Tract in Deficiency States, with Special Reference to the Small Intestine: A Roentgenologic and Clinical Study of Forty Cases, J. A. M. A. **104**:613 (Feb. 23) 1935.

of Columbia University. Table 6 summarizes the principal alterations which were seen in the roentgenograms of twenty-nine patients with sprue, and illustrations from several cases are presented.

Variation in Caliber of the Intestinal Loops.—Variation in the caliber of the intestinal loops occurred most frequently in the ileum, somewhat less frequently in the jejunum and rarely in the duodenum. The greatest variations in caliber were noted in studies of patients with severe sprue. Here the intestinal loops often appeared to be atonic; they were frequently dilated to such a degree that the diameter approached that of

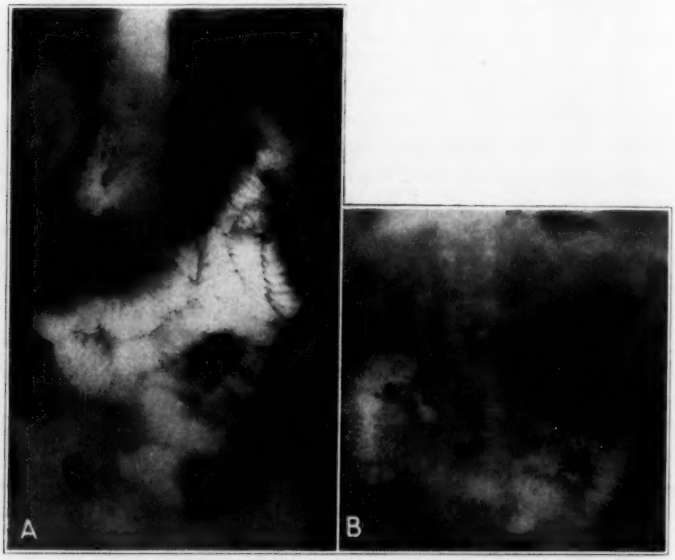

Fig. 3.—*A*, severe sprue (case 4). Note the abnormally dilated small intestine, with striking deviation of the mucosal pattern from normal. *B*, mild sprue (case 29). Note the variation in the caliber of the intestinal loops.

the large bowel (fig. 3 *A*). In other instances the deviation from the normal caliber of the small intestine was less marked, yet there was sufficient variation in caliber to suggest spasticity in certain areas and dilatation in others (figs. 3 *B* and 5 *A*). In the severe form of the disease these changes were found in the jejunum and ileum; in the milder form the ileum alone was involved.

Distortion of the Mucosal Pattern.—Distortion of the mucosal pattern was commonly noted in the jejunum and ileum, less frequently in the duodenum. The most striking changes occurred in the jejunum;

in the cases of milder involvement the delicate feathery pattern of the normal jejunum (fig. 4 *A*) was replaced by a much coarser pattern (fig. 4 *B*), whereas in many of the cases of more severe involvement the valvulae conniventes were markedly thickened and widely separated, giving rise to a picture not unlike that of the normal colon (fig. 3 *A*).

All the patients of group A showed distortion of the mucosal pattern in the jejunum, and all but one showed similar alterations in the ileum. In groups B and C an equal number of patients showed changes in the jejunum and in the ileum.

Segmentation.—Isolated segments of the intestine frequently presented a sausage-like appearance, which was usually observed in the middle and lower portions of the ileum (fig. 5 *A*). This segmental

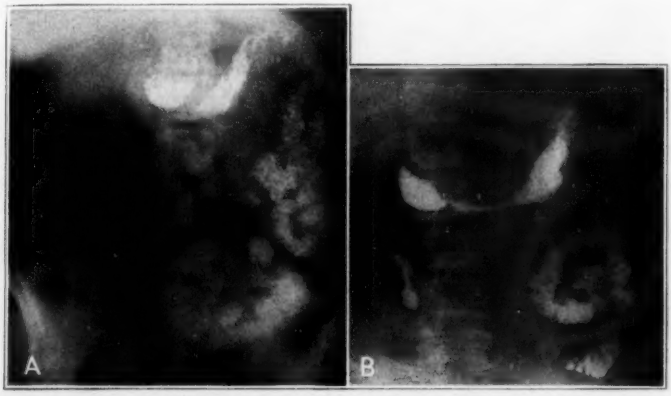

Fig. 4.—*A*, mild sprue (case 32). The essentially normal jejunum should be compared with the appearance in figures 3 *A* and *B* and 4 *B*. *B*, mild sprue (case 29). Note the distortion of the mucosal pattern of the jejunum.

distribution or pocketing of the barium was considered to be due to an irregularity of the movement of the contrast medium. The segmentation was interpreted as caused by alternating areas of spasticity and dilatation of the intestine. This type of segmentation was observed in all patients of groups A and B except one and in some patients of group C. Such a patchy distribution of barium has been observed in other conditions associated with diarrhea.[12]

In addition to the three most common alterations of the small intestine just described, certain other abnormalities were noted. In twelve

12. Mills, R. W.: X-Ray Evidence of Abdominal Small Intestinal States Embodying an Hypothesis of the Transmission of Gastro-Intestinal Tension, Am. J. Roentgenol. **9**:199, 1922.

instances the barium advanced through the small intestine in a divided column (fig. 5 *B*), whereas normally the column is continuous. This separation of the opaque material into two or more columns suggested that the progression was temporarily arrested at one or more points along the intestinal tract. A terminal ileum which seemed to be straighter and more rigid than normal was observed in eleven cases. The roentgenographic picture of the colon was essentially normal in every instance in which a barium enema was given.

Summary of Roentgen Findings.—A distortion of the mucosal pattern and a variation in the caliber of the intestinal loops were the most significant changes observed roentgenographically in the small intestines

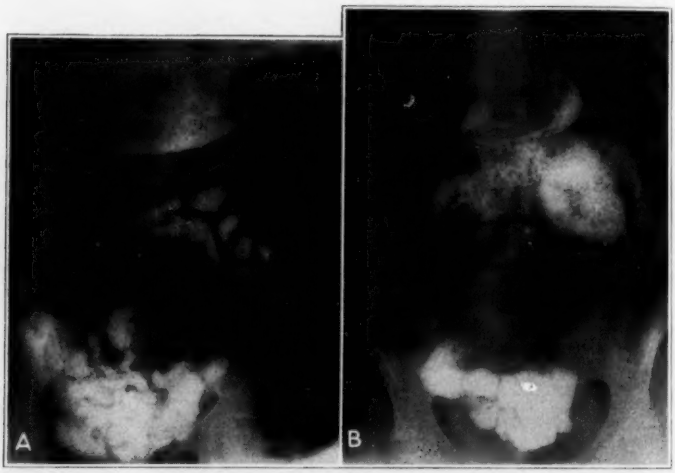

Fig. 5.—*A,* severe sprue (case 1). Note the variation in the caliber of the ileal loops and the segmental distribution of the barium in the ileum. *B,* note the separation of the barium meal into two columns (case 4).

in twenty-nine cases of sprue. All the patients showed these changes in various degrees. In general, the more severe the disease, the more pronounced the morphologic alterations. The roentgenographic findings should not be regarded as pathognomonic of sprue, as no comparisons can be made until more patients with other intestinal disorders have been studied by the same technic. Nevertheless, a correlation appears to exist between the severity of the disease and the extent of the morphologic alterations. Furthermore, these changes can be shown to regress after the use of specific antisprue therapy.

TREATMENT

The results obtainable through the adequate treatment of sprue are convincingly illustrated by this series of thirty-three patients. For the purpose of discussion the therapy employed is most conveniently divided into three phases: (1) treatment before admission to the hospital, (2) treatment during hospitalization and (3) treatment following discharge from the hospital.

1. *Treatment Before Admission to the Hospital* (Table 7).—It is of interest to review briefly the various types of treatment administered to the patients of this series before they were admitted to this hospital. Table 7 summarizes the treatment and results under three separate headings; diet, liver extract administered orally and liver extract administered parenterally.

Of the twenty-seven patients for whom a dietary regimen had been prescribed, twenty-two had been given some form of diet for sprue, that is a diet high in protein and low in carbohydrate and fat. Six received no benefit from this diet, whereas sixteen showed distinct improvement early in the course of the disease. Six of the sixteen patients who improved had been specifically instructed to include whole liver in their diet. Once the symptoms of sprue had been controlled by strict dietary measures, the patients took liberties with their diet or abandoned it entirely. The result was a recurrence of gastro-intestinal and oral symptoms. When such relapses set in, the patients frequently found that diets which had induced remissions in the past were no longer effective. Case 12, described in detail previously, well illustrates such a sequence of events.

Seven patients had received liver extract orally at one time or another during the course of their illness. Four were temporarily improved, whereas three were unimproved.

Liver extract had been administered parenterally to twelve patients. Three showed distinct symptomatic relief. Six were temporarily benefited and, to judge from the subsequent course, would have continued to improve if the parenteral therapy had been continued. In three cases the symptoms were not alleviated, presumably because the amount of liver extract given was too small. For example, one patient (case 12) did well when he received an intramuscular injection of 3 cc. of liver extract every day, yet later he showed no response to an intravenous injection of 2 cc. once a week.

It is apparent that the great majority of the patients in this series had been inadequately treated before they were admitted to the hospital. Temporary remissions had been effected in many cases both by dietary measures and by liver extract, but therapy had not been sufficiently intensive to maintain the patients in good health.

TABLE 7.—*Treatment Before Hospitalization* *

Case	Diet	Result	Liver Extract, Oral	Result	Liver Extract, Parenteral	Result
			Group A			
1	Cooked liver and sour milk (S)	Temp.	3 vials q.d., 14 months	No imp.		
2	Eggs, milk and chopped meat; no starch or carbohydrate (S)	No imp.	.....	.....	2 cc. intramusc. q.d., 5 weeks	No imp.
3	Rice and few vegetables	No imp.				
4	Meat and eggs (S)	Temp.	6 vials q.d., 3 months; 9 vials q.d., 6 months	Temp.		
5	High protein, low carbohydrate and fat (S)	Temp.	.....	.....	2 cc. intramusc. twice a week	No imp.
6	Cereals, eggs, milk, fruit juices, bananas, cream, high protein and cooked liver (S)	Temp.				
7	a. Low residue b. High protein (S)	Temp. No imp.	Exact amount not known	No imp.	Intraven. injections for 3 weeks	Temp.
8	.....	.....	.....	.....	10 intramusc. injections; 4 weekly for short time	Temp.
9	High protein (S)	No imp.				
10	a. Eggs, milk and bananas (S) b. Brown bread and pineapple	Temp. Worse				
			Group B			
11	Coffee, cereal, bread, pork, chicken and some milk	No imp.				
12	Diet for sprue with liver (S)	Temp.	3 vials q.d.	No imp.	a. 3 cc. intramusc. q.d., 5 months b. 2 cc. intraven. weekly	Imp.; tired of treatment No imp.
13	Low starch (S)	Temp.				
14	a. High protein, low fat and carbohydrate (S)	.....	.....	.....	a. Campolon intramusc. q. 2 days, 2 weeks	No imp.
	b. Raw meat and bananas (S) c. High carbohydrate, little fat or protein	No imp.	.....	.....	b. 2 cc. intramusc. 4 q. week, 5 weeks	No imp.
15	a. Liver, meat and fish (S) b. Fish, fruit, vegetables, potatoes, broths, custards and crackers	Temp. Temp.				
16	(S)	Temp.	.....	.....	10 cc. intramusc. twice a week	Imp.
17	Low residue	Slight, temp.				
18	a. 3 qts. of milk, grapefruit juice, rare beef and liver added (S) b. Liver with milk and red meats (S)	Temp.				
19	Eliminated orange juice	Temp.				
			Group C			
20	Eliminated fatty and starchy foods (S)	Temp.				
21	.....	.....	.....	.....	a. 10 cc. intramusc. q. week b. 2 cc. intramusc. twice a week	Temp. Temp.
22	(S)	No imp.	.....	.....	Small amount irregularly	Temp.
23	a. Skimmed milk and strawberries b. Fruits and vegetables with red meat (S)	No imp. Temp.				
24	(S)	No imp.	4 capsules q.d., 6 months	Temp.	39 cc. intramusc. in 2 weeks	Temp.
25	Rare scraped beef and Bulgarian buttermilk (S)	Temp.				
26	Fresh vegetables and meat (S)	Temp.	3 vials q.d., 3 months	Temp.		
27	High protein (S)	Temp.				
28						
29						
30	High meat diet with liver (S)	Temp.	.....	.....	Course of injections every spring and fall	Imp.
31	Low fat-low salt diet	No imp.				
32	.....	.....	2 courses of treatment	Temp.	4 intramusc. injections in 2 weeks	Temp.
33						

* (S) signifies diet for sprue; temp., temporary improvement; imp., improvement; no imp., no improvement; intramusc., intramuscularly, and intraven., intravenously.

2. *Treatment During Hospitalization* (Table 8).—The three chief therapeutic measures employed in the treatment of these patients in the hospital were: (*a*) rest in bed, (*b*) a diet for sprue and (*c*) liver extract given parenterally.

(*a*) Rest in Bed: Complete rest in bed was of course essential in the cases of severe sprue and also furnished a useful adjunct to the more specific forms of therapy in the cases of a milder degree of involvement. It was not uncommon to find that a patient required more intensive therapy when ambulatory than when at rest in bed. Undue fatigue appeared to play a prominent rôle in the precipitation of relapses.

(*b*) Diet for Sprue: The diet for sprue as used in this clinic was essentially high in protein and low in carbohydrate and fat. Emphasis was placed on the taking of large amounts of rare red meat. The dietary regimen is presented in table 9. Practically all the patients received this diet unless the severity of their condition made such a measure impossible. Then the patient was given nothing but ground meat and milk until he could partake of a more liberal fare.

Three patients in group C were treated with the diet for sprue alone and became practically symptom free on this regimen. One patient was not treated, as he was referred to this hospital for diagnostic study only. For the remaining twenty-nine patients the dietary treatment was not effective until it was supplemented with injections of liver extract. No patient with sprue of moderate or severe degree was seen for whom dietary treatment alone brought about complete amelioration of symptoms.

(*c*) Liver Extract: Unless otherwise specified, solution of liver extract for parenteral use, both intramuscular and intravenous, was prepared from liver extract [4] which met the standard given in "New and Nonofficial Remedies." The concentration of the solution for intramuscular injection was twice that of the solution for intravenous use. The solutions were made up so that 10 cc. of the intramuscular preparation or 20 cc. of the intravenous preparation contained the amount of extract derived from 50 Gm. of whole liver. The maximal and usual dose of the intramuscular extract given at one time was 10 cc.; of the intravenous extract, 20 cc. An intramuscular injection was sometimes productive of soreness and burning at the site of injection but was rarely followed by systemic reactions. The intravenous injections were occasionally followed by chills, fever, flushing, headache, nausea or urticaria. No reactions so severe as to require cessation of treatment were observed.

The total amount of liver extract injected into a given person during the period of hospitalization depended on the severity of the symptoms, the grade of anemia and the rapidity of the response to therapy. All the

TABLE 8.—*Treatment*

Case	During Hospitalization				After Discharge		Total Period of Observation
	Diet	Liver Extract, Intramuscular	Liver Extract, Intravenous	Result	Liver Extract	Comments	
				Group A			
1	No bread or potatoes	20 cc. 1 day 10 cc. q.d., 9 days 2 cc. q.d., 6 days 10 cc. q.d., 9 days	....	..... Improvement Diarrhea Improvement	10 cc. q. 2 weeks	Well	4½ yr.
2	Sprue	10 cc. q.d., 3 days 10 cc. q. 2 weeks 10 cc. q. 10 days	.....	Improvement	20 cc. q. month	Returned to Puerto Rico; symptom free	4½ yr.
3	Sprue	.....	20 cc. q.d., 30 days	Improvement	10 cc. q. 2 weeks	Well	3½ yr.
4	Sprue	10 cc. q.d., 10 days	20 cc. q.d., 5 days	Improvement	10 cc. q. week 10 cc. twice a week	Discontinued liver; had relapse in 2 months; readmitted; now symptom free	3½ yr.
5	Sprue	10 cc. q.d., 4 days	20 cc. q.d., 10 days	Improvement	10 cc. q. 2 weeks	Symptom free	3 yr.
6	Sprue	10 cc. q.d., 30 days	20 cc. q.d., 20 days	Improvement temporarily	.....	Died of tuberculous peritonitis	6 mo.
7	Sprue	.....	20 cc. q.d., 5 days	Improvement	Irregular	Died of carcinoma of pancreas	1¾ yr.
8	Light	10 cc. q.d., 10 days	.....	Improvement	10 cc. q. 2 weeks	Relief of symptoms	4 yr.
9	Sprue	.....	20 cc. q.d., 13 days	Improvement	.....	Discharged against advice; not followed	2 mo.
10	Sprue	10 cc. q. 2 days for 10 injections	.....	Improvement	10 cc. q. week	Symptom free	1 yr.
				Group B			
11	Sprue	10 cc. q.d., 10 days	.....	Improvement	10 cc. q. week	Well	1¼ yr.
12	Sprue	.....	20 cc. q.d., 8 days	Improvement	20 cc. intravenously q. 7-10 days; twice weekly	Fairly well at first; symptom free on treatments twice weekly	2¼ yr.
13	Sprue	10 cc. q.d., 7 days	.....	Improvement	10 cc. twice weekly	Not improved	2¼ yr.
14	Sprue	.....	20 cc. q.d., 11 days	Improvement	10 cc. q. 10 days	Well	2¼ yr.
15	Sprue	5 cc. q.d., 5 days	20 cc. q.d., 8 days	Improvement	10 cc. q. 2 weeks	Returned to China; well	3¼ yr.
16	Sprue	.....	20 cc. q.d., 5 days	Improvement	10 cc. q. week	Well	2½ yr.
17	Sprue	10 cc. q.d., 8 days	20 cc. q.d., 10 days	Improvement	.....	Not followed in clinic	4 mo.
18	Sprue	10 cc. q.d., 7 days	.....	Improvement	10 cc. q. 2 weeks	Returned to Puerto Rico; well	2¼ yr.
19	Sprue	.....	20 cc. q.d., 20 days	Improvement	.....	Died of sprue in another hospital without therapy	1 yr.

TABLE 8.—*Treatment—Continued*

Case	Diet	During Hospitalization: Liver Extract, Intramuscular	During Hospitalization: Liver Extract, Intravenous	Result	After Discharge: Liver Extract	After Discharge: Comments	Total Period of Observation
				Group C			
20	Sprue	.....	.....	.....	.....	Not treated in hospital	2 mo.
21	Sprue	3 cc.* q.d., 13 days	.....	Improvement	10 cc. q. 2 weeks	Returned to Puerto Rico; well	4 yr.
22	Sprue	10 cc. q. week	.....	Improvement	10 cc. q. week	Well	2 yr.
23	Sprue	10 cc. q.d., 5 days	.....	Improvement	10 cc. twice weekly; 10 cc. q. week	Well	2¼ yr.
24	Sprue	10 cc. q.d., 6 days 10 cc. thrice weekly, 3 weeks	20 cc. q.d., 5 days	Improvement	10 cc. q. 2 weeks	Well; returned to China	1¼ yr.
25	Sprue	10 cc. for 4 injections	.....	Improvement	10 cc. q. 2 weeks	Well	9 mo.
26	Light	10 cc. for 2 injections	.....	Improve-	.....	Advised to return to China; not followed	1 mo.
27	Sprue	.....	.....	Improvement	.....	Well on diet	1 yr.
28	Sprue	.....	.....	Improvement	.....	Well on diet	3 mo.
29	Sprue	10 cc. q.d., 8 days	.....	Improvement	10 cc. q. 2 weeks	Well	1 yr.
30	Sprue	10 cc. q. week	.....	Improvement	10 cc. q. week	Well	1 yr.
31	Sprue	10 cc. q. 2 days, 12 injections	.....	Improvement	10 cc. q. 2 weeks	Well	1½ yr.
32	Sprue	10 cc. q.d., 4 days	.....	Improvement	10 cc. q. 2 weeks	Well	1½ yr.
33	Sprue	.....	.....	Improvement	.....	Fairly well on diet alone	6 mo.

* Liver extract-Lederle (N. N. R.) was used.

patients in groups A and B and ten patients in group C received parenteral injections of liver extract during their stay in the hospital. The amount of liver extract given to patients of groups A and B was greater than that given to patients of group C, as the former had a more severe form of the disease. One patient (case 6) received daily injections for fifty days with only temporary relief of his symptoms; this patient died later of tuberculous peritonitis. Another patient (case 3) received daily intravenous injections for thirty days. The majority of patients in the first two groups required daily injections over periods of from five to twenty days, whereas shorter courses of parenteral therapy usually brought about complete relief of symptoms in the patients in group C. The importance of intensive liver extract therapy in the treatment of

cases of severe sprue has already been emphasized.[13] Too much stress cannot be laid on the fact that much larger amounts of liver extract are generally necessary to control the symptoms of sprue than are required to induce a remission in a case of severe pernicious anemia.

The alleviation of the various symptoms of sprue with combined dietary and liver extract therapy was on the whole phenomenal. The

TABLE 9.—*Diet for Sprue*

Breakfast
Toast, 1 thin slice with a small piece of butter
Fresh fruit, large serving
Eggs, 2, prepared in any manner desired
Milk, at least 1 large glass (this may be heated and used in place of cream for coffee or may be made into cocoa)
Luncheon
Meat, large serving (½ pound at least)
Vegetables, 2, or 1 vegetable and salad
Milk puddings, gelatin, ice-cream or fresh fruit
Crackers (2 only) with cheese
Milk, 1 glass
Dinner
Fruit cocktail or tomato juice
Beef broth or any cream soup (make cream soups with milk instead of cream and omit butter)
Meat, large serving (½ pound at least)
Vegetables, 2 at least
Desserts, as for lunch
Milk, 1 glass
Egg-nogs, milk or fresh fruit may be eaten between meals
The diet should consist largely of protein:
Meat: Meat should always be lean and rare Beef, lean, either roast or steak Lamb, lean, either roast or chops Ham, lean Liver, tongue, heart, kidney or sweetbreads Fish, any fresh fish Chicken Lobster, crab or oysters
Milk and milk products: milk, buttermilk and American and cottage cheese
Eggs: prepared in any manner desired
All fatty foods should be avoided: butter, cream, lard, olive oil and all oil salad dressing, avocado pears, pie, pastry and all foods fried in fat
All starchy foods should be avoided: potatoes, beans, corn, bread, cereals, cake and candy

gastro-intestinal symptoms—diarrhea, flatulence, anorexia and nausea—cleared up entirely in all but two patients treated in the hospital. When these symptoms were under control, the patients began to gain weight at a rate which was often astounding in view of the dietary restriction of carbohydrate and fat. Soreness of the tongue and mouth disappeared, aphthous lesions healed and in those patients who showed papillary atrophy regeneration of the papillae took place.

13. Rhoads, C. P., and Miller, D. K.: Intensive Liver Extract Therapy of Sprue, J. A. M. A. **103**:387 (Aug. 11) 1934.

No less striking was the improvement in the blood picture of those patients who had anemia. The red blood cell count, hemoglobin value and white blood cell count all returned toward normal levels, as did the mean corpuscular volume and the color index.

Thus it is apparent that the various clinical manifestations of sprue, both mild and severe, were dramatically alleviated in the great majority of cases by the institution of adequate therapy. In the cases of more severe involvement therapy was necessarily intensive at first, whereas in the cases of milder involvement several injections of liver extract, or at times dietary measures alone, sufficed to render the patients symptom free.

(*d*) Adjunctive Therapeutic Measures: In addition to rest in bed, a diet for sprue and liver extract, certain other therapeutic measures were indicated in a small percentage of patients. These measures were blood transfusion, calcium salts and iron. If the anemia is so severe as to jeopardize the patient's life, blood transfusion should be given. Only one patient in this series (case 2) required transfusion. Calcium salts should be administered both orally and parenterally to patients with tetany, muscle cramps or osteoporosis. Two patients (cases 6 and 7) who had tetany were given intravenous injections of calcium chloride during the acute stage; later they were given calcium gluconate by intramuscular injection. Muscle cramps were relieved by the oral administration of calcium chloride in case 4. The addition of intramuscular injections of calcium to liver extract therapy afforded more complete relief from gastro-intestinal symptoms in a few cases. Occasionally the anemia of sprue was microcytic, or the blood picture changed from a macrocytic to a microcytic type after treatment with liver extract. In such cases iron, in the form of ferrous sulfate or iron and ammonium citrates, was given as a supplement to liver extract therapy.

3. *Treatment Following Discharge from the Hospital* (Table 8).—Perhaps more important than the alleviation of the acute symptoms is the maintenance of patients with sprue in good health over a prolonged period. Data are available for twenty-nine of the thirty-three patients over periods of from three months to four and one-half years after discharge.

Three patients of this series have died. One patient (case 6) died of tuberculous peritonitis after six months, and another (case 7) died of carcinoma of the pancreas after twenty-one months. It is of interest that the symptoms of both patients were temporarily relieved by anti-sprue therapy. One patient (case 19) died of sprue in another hospital, where he was not given specific therapy.

One patient (case 13) continued to have attacks of diarrhea, cramps and flatulence in spite of diet for sprue and injections of liver extract

twice a week. The addition of liver extract orally and injections of calcium gluconate alleviated the symptoms to a certain extent but failed to afford complete relief. For this reason the patient was readmitted to the hospital for further study. No amebas were found in the stools, and culture revealed no pathogenic organisms. With rest in bed in addition to dietary and liver extract therapy, the diarrhea and cramps ceased, only to recur when the patient resumed her secretarial work. This is the only patient with tropical sprue whose symptoms have not been controlled by the antisprue regimen which has been described.

Another patient (case 33) has been only "fairly well" on the diet for sprue alone. To judge from the course of the other patients studied it is possible that an occasional injection of liver extract would render this patient free from symptoms.

The remaining twenty-four of the twenty-nine patients for whom adequate follow-up data are available have remained practically symptom free with continued antisprue therapy. Five of these patients have returned to tropical countries without a recurrence of symptoms. Two of the twenty-four have remained essentially well on the diet for sprue alone. The other twenty-two patients have required injections of liver extract at regular intervals. One patient is given an intravenous injection of 20 cc. twice a week and another an intramuscular injection of 10 cc. twice a week. Seven patients receive a single intramuscular injection of 10 cc. once a week, twelve patients receive an intramuscular injection of 10 cc. every two weeks and one patient remains symptomatically well with one intramuscular injection a month.

The interval that is allowed to elapse between injections of liver extract must be ascertained for each patient. Injections should be given at sufficiently frequent intervals to prevent the recurrence of gastro-intestinal symptoms. One patient (case 1) who has been followed for four years may be taken as an illustration of this principle. During the first year after discharge from the hospital this patient suffered from recurrent gastro-intestinal symptoms which began about ten days after an injection of liver extract; therefore she was treated once a week. More recently she has found that she remains free from symptoms for nearly three weeks after an injection; accordingly the interinjection interval has been increased to two weeks.

The intimate relationship that exists between the injection of liver extract and the cessation of gastro-intestinal symptoms has been recognized by many patients. A patient who has symptoms as a result of transgressing the safe interval between treatments usually experiences complete relief from these symptoms within twenty-four hours after an injection of liver extract. Furthermore, a number of patients have found through repeated trials that soon after a treatment with liver

extract they may take many liberties with their diet with impunity, whereas during the latter part of the interinjection interval they must adhere strictly to the diet for sprue in order to prevent the recurrence of gastro-intestinal symptoms.

Both mental and physical fatigue were often responsible for the onset of symptoms in these patients. During periods of stress the frequency of injections had to be increased. Case 30 serves to illustrate just such a situation. This patient suffered from a "nervous breakdown" several weeks after she had been rendered free from symptoms of sprue by specific therapy. During a period of two weeks she was upset mentally, ate little and received no liver extract. At the end of this period she had a typical relapse of sprue with diarrhea, flatulence and a sore red tongue. These symptoms cleared up rapidly when treatment with liver extract was resumed.

The question naturally arises as to whether the patient with sprue can ever abandon specific therapy entirely without suffering a relapse. All that can be said in answer to this question is that those patients who have voluntarily discontinued therapy have suffered relapses; this occurred, for example, in case 4, described in detail under group A. The majority of these patients have been unwilling to abandon their therapeutic regimen for fear of suffering a relapse. It is evident that the well-being of a patient with sprue is dependent on the regulation and maintenance of this specific regimen. The amount of liver extract which is necessary to prevent the recurrence of gastro-intestinal symptoms is far greater than that which is required to maintain normal blood values. Hence the basic principle in the treatment of sprue is the administration of an adequate amount of liver extract at sufficiently frequent intervals to prevent the recurrence of abdominal discomfort, flatulence and diarrhea.

SUMMARY AND CONCLUSIONS

A series of thirty-three patients with sprue has been studied. Twenty-nine of these patients have been followed in the clinic after discharge from the hospital. The patients have been divided into three groups on the basis of certain symptoms and clinical findings at the time of entry into the hospital. Ten patients presented the classic picture of severe sprue with diarrhea and anemia. Nine patients had diarrhea but no anemia, while the remaining fourteen complained only of abdominal discomfort and flatulence. The symptomatology, the blood findings and the results of gastric analyses for these patients have been presented in detail, together with abstracts of illustrative cases.

Roentgen study of the small intestine was made for twenty-nine of these patients, and morphologic alterations of the small intestine were observed in all, these changes varying directly with the severity of

the disease. The most significant abnormalities were a distortion of the mucosal pattern and a variation in the caliber of the intestinal loops. These roentgenographic changes are not regarded as being pathognomonic of sprue, since not enough studies of the small intestine have been made in cases of other gastro-intestinal disorders for purposes of comparison.

Treatment before, during and after hospitalization has been discussed in detail. The great majority of the patients experienced complete symptomatic relief once adequate therapy had been instituted. Moreover, these patients have been maintained in excellent health over long periods by means of a relatively simple therapeutic regimen. Five patients have returned to tropical countries without recurrence of symptoms. It must be emphasized that no patient has discontinued specific therapy entirely without suffering a relapse. The maintenance of a diet for sprue in addition to liver extract therapy gives a patient more complete relief of gastro-intestinal symptoms than does liver extract given parenterally alone. The frequency of injections of liver extract must be worked out for each patient, the prevention of intestinal dysfunction serving as a guide to the amount of therapy to be given.

ACUTE BISMUTH POISONING, WITH RECOVERY

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Bismuth toxemia, fortunately, is now rare. Five years ago one of us (A. E. O.) prepared an alkaline solution of bismuth and potassium tartrate [1] for use as a cytographic medium and found it roentgenologically satisfactory in more than one hundred cases and without toxic effect.[2] Subsequently, after the use of this substance prepared elsewhere, we observed two patients with acute bismuth toxemia, and we are reporting these cases because the symptoms and course were unusual.

The chief initial symptom was oliguria or anuria, and it was not until characteristic stomatitis developed later that bismuth toxemia was suspected. Experimental studies on animals have demonstrated that toxic amounts of bismuth salts will cause a disturbance in renal function,[3] including azotemia and a renal lesion most noticeable in the tubular cells.[4] A fatal case in which there was anuria with marked retention of urea in the blood was reported by Aubertin and Destouches [5] in 1927. Dowds in 1936 made a report of three fatal cases with necropsies.[5a] Early recognition of the condition and immediate institution of adequate therapeutic measures are therefore important to insure renal recovery.

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REPORT OF CASES

CASE 1.—The patient, a man aged 63, a foreman in a railroad roundhouse, was admitted to the clinic on July 12, 1932. In 1917 he began to have urinary frequency and urgency, which continued for one year; chills and fever due to a urethral abscess then developed which finally required perineal drainage. Intermittent recurring chills and fever followed, with recurrence of the abscess in the perineum. About 1928 the patient began having "bladder treatments," and he became practically free from symptoms for one and a half years prior to his admission to the clinic. The last cystoscopic examination was made five months previous to entry.

On physical examination at the clinic he weighed 213 pounds (96.8 Kg.). A perineal scar was present, as was also a moderate degree of prostatic hypertrophy. The blood pressure in millimeters of mercury was 140 systolic and 90 diastolic. The value for hemoglobin was 16.7 Gm. per hundred cubic centimeters, and the erythrocytes numbered 4,760,000 and the leukocytes 7,500 per cubic millimeter of blood. The serologic test for syphilis gave a negative result. There was a 55 per cent excretion of phenolsulfonphthalein in two hours. A roentgenogram of the kidneys indicated that the size and outline were normal. Urinalysis showed the specific gravity of the urine to be 1.027; it contained albumin (grade 1), no sugar and 50 pus cells per microscopic field.

On the first day (July 14) 150 cc. of the bismuth solution was injected into the bladder and left there for from five to ten minutes while the cystogram was taken; it was then expelled as completely as possible. The cystogram revealed a normal vesical outline. A diagnosis was made of bilateral, median, intra-urethral prostatic hypertrophy, moderate prostatic fulness, chronic cicatricial urethritis and chronic bilateral pyelonephritis. There was no residual urine or any symptoms of discomfort. It seemed probable that the previous abscess was of prostatic origin. Toward evening of this day the patient noticed that the volume of urine was gradually decreasing. The last specimen was voided at 2 a. m. on July 15. He was then sent to the hospital, and treatment for oliguria was commenced. The next day, July 16, the output of urine amounted to only 20 cc., and the patient vomited 500 cc. of fluid.

Between July 15 and August 7 the temperature ranged from 98 to 100.8 F. and the pulse rate from 70 to 120 beats per minute. Vomiting continued for a period of eleven days (July 16 to 27). During this period the blood pressure ranged from 125 to 170 systolic and 60 to 90 diastolic. The ocular fundi were normal. Fluid given intravenously from July 15 to August 10 consisted of solutions containing 10 per cent dextrose, 1 per cent sodium chloride and 5 per cent sodium bicarbonate (table 1).

On July 17, the fourth day after the patient's admission to the hospital, an emergency cystoscopic examination was carried out, spinal anesthesia being employed. No urine was observed flowing from the left ureter; however, a few drops were seen coming from the right ureter. The patient had vomited a total of 1,150 cc. of fluid in the past two days. On July 18 slight edema of the lower part of the legs was noticed. The patient was drowsy; oliguria and almost complete anuria had persisted for four days. Dr. Cabot carried out bilateral (simultaneous) renal decapsulation with the patient under spinal anesthesia. Both kidneys were enlarged, firm and rather granular, suggesting chronic nephritis (for chemical studies of the blood see table 1).

On the eighth day after entry (July 21) the patient was irrational at times; the blood pressure was 140 systolic and 70 diastolic. On the next day there was

TABLE 1.—*The Data for the First Patient*

Day of Observation	Intake of Fluid: Intravenous: Sodium Bicarbonate, Gm.	Intake of Fluid: Intravenous: Sodium Chloride, Gm.	Intake of Fluid: Intravenous: Dextrose, Gm.	Intake of Fluid: Intravenous: Total, Cc.	Intake of Fluid: Total Intake of Fluid, Cc.	Urine†: Volume, Cc.	Urine†: Protein, Grade	Urine†: Casts, Grade	Urine†: Erythrocytes, Grade	Urine†: Leukocytes, Grade	Blood: Hemoglobin, Gm. per 100 Cc.	Blood: Erythrocytes, Millions per Cu. Mm.	Blood: Urea, Mg. per 100 Cc.	Blood: Creatinine, Mg. per 100 Cc.	Blood: Serum Sulfate, Mg. per 100 Cc.	Blood: Plasma Chloride, Mg. per 100 Cc.‡	Blood: Plasma Carbon Dioxide Combining Power, Vol.%	Comment
*	..	....	...	.....	.....	.....	1	..	..	3	16.7	4.76	...	....	...	...	..	Phthalein excretion, 55 per cent
1	..	....	...	.....	.....	.....	..	..	..	..	....	....	...	....	...	...	..	Cystogram: normal vesical outline
2	..	18.0	....	2,000	3,400	0	..	..	..	..	....	....	...	....	...	...	..	
3	..	29.0	200	3,000	5,075	20	..	..	..	..	....	....	90	4.3	...	...	..	Emesis, 500 cc.
4	..	13.5	....	1,500	3,305	125	..	..	..	..	....	....	100	7.8	...	...	..	Emesis, 600 cc.
5	..	13.5	150	1,500	3,850	68	..	..	..	..	....	....	124	9.3	...	...	..	Bilateral renal decapsulation; emesis, 550 cc.
6	..	13.5	250	2,500	3,150	50	..	..	..	..	13.3	3.77	132	11.2	...	...	..	Bleeding from gums
7	25	0.9	60	900	2,180	5+	2	0	3	3	....	....	154	11.6	...	511	32	
8	..	27.2	200	2,800	3,330	9	..	..	..	..	....	....	...	....	...	...	..	Salyrgan, 0.5 cc.
9	25	23.5	100	3,000	4,700	80	..	..	..	..	13.1	3.65	200	12.0	...	528	43	Salyrgan, 0.5 cc.
10	..	5.0	150	1,500	2,250	400	..	..	..	..	....	....	208	12.4	...	495	47	
11	..	4.5	250	3,000	4,060	850+	..	..	..	..	....	....	...	....	...	...	..	Stomatitis; twitching of muscles
12	..	15.4	250	3,100	3,500	2,000+	2	0	1	1	....	....	180	14.0	...	462	41	Colon bacilli in urine
13	..	15.0	300	3,000	4,000	1,900+	..	..	..	..	11.4	2.80	234	13.2	...	479	35	
14	..	14.5	250	3,000	4,000	2,400	..	..	..	..	....	....	231	13.2	...	479	33	
23	..	14.4	...	1,600	5,200	4,640	..	..	..	..	....	....	105	6.0	8.7	594	37	
40	..	....	...	.....	3,000	2,700	..	..	..	..	....	....	40	....	7.1	619	54	
3¼ years later							0	0	0	2	17.4	4.37	26	....	5.5	...	..	Urea clearance, 53 cc.; sulfate clearance, 40 cc.

* Data obtained on entry.
† Variation of the specific gravity during toxemia, 1.004 to 1.008.
‡ Calculated as sodium chloride.

considerable drainage of fluids (500 cc.?) through the wounds in the loin. On the eleventh day some twitching of the facial muscles and also ulcerative stomatitis and swelling of the tongue were noted. A diagnosis of possible bismuth poisoning was made. On the twelfth day cultures of the urine revealed colon bacilli. The blood pressure was 130 systolic and 65 diastolic on July 31. In the last week of July the patient's condition steadily improved. During the phase of acute oliguria, edema was never marked and was limited to the dependent parts of the back and legs. On August 30, forty-eight days after the onset of toxemia, the patient was dismissed. His general condition was very satisfactory.

Three and a fourth years later (Oct. 24, 1935) the patient felt well. He weighed 211 pounds (96 Kg.). His general physical condition was satisfactory, and his blood pressure was 190 systolic and 110 diastolic. The eyegrounds revealed mild sclerosis of the retinal arterioles. Urinalysis did not show albumin or sugar, but there were still 50 pus cells per microscopic field (table 1). The patient still had chronic pyelonephritis, with slight reduction of renal function. The hypertension was of the essential type.

Case 2.—The patient, aged 40 years, a life insurance agent, was admitted on Aug. 4, 1932. Two weeks previously he began to have attacks of severe pain in the right lumbar region, which spread slightly around over the iliac crest to the right lower quadrant of the abdomen. There were mild chills and a little fever, and the pain lasted three or four hours. His local physician shortly afterward found microscopic quantities of blood in the urine. The patient's second attack was similar to the first and occurred one week before his admission to the clinic; it also lasted four hours, and microscopic quantities of blood were again passed. No stones were passed during or after either attack. Jolting when riding in an automobile caused a dull ache in the right lumbar region.

On physical examination the patient's weight was 151 pounds (68.6 Kg.); his blood pressure was 130 systolic and 80 diastolic. There was no edema. The value for hemoglobin was 17.5 Gm. per hundred cubic centimeters, and the erythrocytes numbered 4,520,000 per cubic millimeter. The urea content of the blood was 26 mg. per hundred cubic centimeters. The urine had a specific gravity of 1.010; it contained no albumin or sugar. There were 10 leukocytes per microscopic field but no erythrocytes. A roentgenogram disclosed a small calculus in the region of the upper third of the right ureter.

On August 8 from 7 to 10 cc. of the bismuth solution was injected through a ureteral catheter into the right ureter and renal pelvis. It remained there for ten or fifteen minutes and then was allowed to drain off through the catheter. A pyelogram of the right kidney was made, and the right ureter showed angulation near the sacro-iliac synchondrosis. A diagnosis of calculus in the right ureter was made. After cystoscopic examination the patient vomited 800 cc. of fluid, and the next day, 450 cc.

On the third day (August 10) nausea and vomiting continued; emesis of 950 cc. brought the total up to 2,200 cc. for the first three days. There was acute necrotic gingivitis. On August 11 there were still nausea and vomiting, some hiccup and oliguria, 80 cc. of urine having been passed in twenty-four hours (table 2). The next day the patient's mouth became sore, his gums were blue and bismuth poisoning was suspected. On August 13 solution of sodium thiosulfate was given intravenously. His blood pressure was 170 systolic and 80 diastolic. The gums continued to be sore the next day, and ulcerating stomatitis was present. The blood pressure on this day was 145 systolic and 90 diastolic.

TABLE 2.—*The Data for the Second Patient*

Day of Observation	Intake of Fluid: Intravenous: Sodium Bicarbonate, Gm.	Intake of Fluid: Intravenous: Sodium Chloride, Gm.	Intake of Fluid: Intravenous: Dextrose, Gm.	Intake of Fluid: Intravenous: Total, Cc.	Total Intake of Fluid, Cc.	Urine†: Volume, Cc.	Urine†: Protein, Grade	Urine†: Casts, Grade	Urine†: Erythrocytes, Grade	Urine†: Leukocytes, Grade	Blood: Hemoglobin, Gm. per 100 Cc.	Blood: Erythrocytes, Millions per Cu. Mm.	Blood: Urea, Mg. per 100 Cc.	Blood: Creatinine, Mg. per 100 Cc.	Blood: Plasma Chloride, Mg. per 100 Cc.‡	Blood: Plasma Carbon Dioxide Combining Power, Vol.%	Comment
*	..	....	...	.....	.....	.....	0	0	0	1	17.5	4.52	26	....	...	..	Roentgenogram of kidneys, ureters, bladder; small ureteral stone on right
1	..	....	...	.....	.....	...	..	..	..	..	....	....	...	....	...	..	Pyelogram of right kidney
3	..	13.4	...	1,500	3,900	80	..	..	..	..	....	....	...	....	...	..	Acute gingivitis
4	..	13.4	...	1,500	4,100	500	3	0	0	4	....	....	132	9.0	...	..	
5	..	13.4	...	1,500	4,300	500	2	1	0	0	....	....	142	....	462	39	Blue gums
6	..	13.4	...	1,500	4,500	510	..	..	..	..	....	....	...	....	...	..	Sodium thiosulfate, 1 Gm.§
7	..	....	...	.....	2,600	500	..	..	..	..	....	....	...	....	...	..	Stomatitis
8	..	16.2	...	1,800	3,900	350	..	..	..	..	....	....	165	14.4	...	..	
9	25	....	200	2,500	2,900	460	1	2	0	0	....	....	...	....	...	..	Ureteral stone passed
10	..	....	187	1,875	2,675	1,600	2	1	3	1	....	....	189	15.2	453	43	Sodium thiosulfate, 1 Gm.§
11	..	3.6	100	1,400	2,155	2,240	..	..	..	..	....	....	162	16.0	479	46	
12	..	10.0	100	1,000	3,500	4,200	..	..	..	..	....	....	177	16.0	...	..	Sodium thiosulfate, 1 Gm.§
13	..	4.5	100	1,500	3,910	4,900	2	0	0	0	....	....	171	15.2	495	48	
14	..	1.0	100	1,120	3,720	5,140	..	..	..	..	....	....	...	....	...	..	
15	..	....	...	.....	3,600	4,600	..	..	..	..	....	....	141	11.2	...	..	
16	..	10.0	...	1,000	3,900	4,220	..	..	..	..	....	....	162	8.4	511	38	
17	..	....	...	.....	2,900	3,580	..	..	..	..	....	....	120	6.0	...	..	
22	..	....	...	.....	.....	.....	..	..	..	..	....	....	36	....	...	..	
3½ years later											....	....	...	....	...	..	Wrote that health was excellent

* Data obtained on entry.
† Variation of the specific gravity during toxemia, 1.004 to 1.010.
‡ Calculated as sodium chloride.
§ Ten cubic centimeters of 10 per cent solution injected intravenously.

On August 16 the patient passed a ureteral stone. Daily readings of the blood pressure taken from August 16 to 24 showed variations, the systolic pressure being from 110 to 170 and the diastolic from 60 to 100 mm. of mercury. On August 19 slight edema of the scrotum and inner portions of both thighs appeared. Sodium thiosulfate was given intravenously. The gums were still sore and the temperature had varied since the onset of toxemia from 98 to 101 F. On August 29, twenty-two days after the onset of toxemia, the patient felt well, the urinary output was satisfactory and the value for blood urea was 36 mg. per hundred cubic centimeters.

On Dec. 30, 1935, approximately three and a half years after the acute toxemia, the patient wrote that he was in excellent health.

COURSE OF TOXEMIA

The acute toxemia in these two cases was characterized by the rapid development of oliguria or anuria within from twenty-four to forty-eight hours after the injection of the bismuth solution. Oliguria was accompanied with nausea and vomiting. Three or four days after the onset, bleeding from the gums and stomatitis developed, but discoloration of the buccal mucous membrane was not evident for several days. The serious disturbance of renal function was accompanied with only minor changes in the amount of protein and sediment in the urine; albumin (grade 2) was present, and there were a few hyaline and granular casts. Erythrocytes were present in the urine of the first patient after renal decapsulation and in the urine of the second patient after passage of the ureteral calculus. The development of azotemia was rapid, and by the fourth day in the second case the values for blood urea and creatinine had risen to 132 and 9 mg. per hundred cubic centimeters respectively. The values for the first patient were slightly lower. Azotemia continued for a period of approximately three weeks, the maximal concentration of urea and creatinine in the blood being 234 and 14 mg. per hundred cubic centimeters, respectively, in the first case and 189 and 16 mg., respectively, in the second. During the period of oliguria and nitrogen retention a moderate decrease in the bicarbonate reserve of the plasma and a decided fall in the chloride concentration of the plasma occurred. Comparable findings have been reported in cases of poisoning due to mercury bichloride [6] and chromium trioxide [7] and of other types of acute renal insufficiency.[8]

At the height of the toxemia the first patient became irrational and twitchings of the facial muscles lasted for several hours. The gradual

6. Lewis, D. S., and Rivers, T. M.: Chemical Studies on a Case of Bichloride Poisoning, Bull. Johns Hopkins Hosp. **27**:193-201 (July) 1916.

7. Major, R. H.: Studies on a Case of Chromic Acid Nephritis, Bull. Johns Hopkins Hosp. **33**:56-61 (Feb.) 1922.

8. Keith, N. M., and Thomson, W. W. D.: War Nephritis: A Clinical, Functional, and Pathological Study, Quart. J. Med. **11**:229-266 (April) 1918.

development of dependent edema was due in part to the large intake of water and sodium chloride and the small output of urine. With resumption of an adequate urinary output, the edema rapidly disappeared. The temperature was usually normal, although in each case it rose on one occasion to 101 F., a rise which may have been due to stomatitis. Daily estimations of the blood pressure were made, and the systolic and diastolic pressures were usually within normal limits. The reason the systolic blood pressure rose to 170 mm. of mercury once in each case is difficult to explain. From three to six weeks after the onset the urea content of the blood reached a normal concentration, and the patients appeared and felt well. The course of the acute renal insufficiency in these cases was similar to that due to mercury bichloride and other agents toxic to the renal parenchyma. Raiziss and Brown [9] noted in a study of the toxicity of bismuth in rabbits that recovery of normal renal function occurred within approximately one month after a toxic dose was received.

Both of our patients were in excellent general health three years later. The first patient returned at this time, and renal function was found to be satisfactory.

TREATMENT

At the onset of the toxemia our therapeutic objectives were to increase renal excretion and prevent dehydration. Because of vomiting, much of the fluid necessarily was injected intravenously. The solutions given were 1 per cent sodium chloride, from 5 to 10 per cent dextrose and 5 per cent sodium bicarbonate, and the daily amounts injected were from 1,000 to 3,000 cc. In our opinion these intravenous injections of appropriate fluid constituted the most important therapeutic measure. In the first case the injection of a small amount of salyrgan on two occasions had no apparent beneficial or harmful effect. Bilateral renal decapsulation did not cause an immediate increase in the volume of urine, nor was an adequate renal output restored until six days after the operation. In the second case the injections of sodium thiosulfate did not appear to affect the toxemia.

TOXICITY OF BISMUTH SOLUTION

In the first case there is the possibility that a considerable portion of the 150 cc. of bismuth solution that was injected into the bladder may have entered the vascular system. In such an event the actual

9. Raiziss, G. W., and Brown, H.: Toxicity and Reactions Caused by Arsphenamin and Neo-Arsphenamin: The Effect of Organic Compounds of Arsenic, Mercury and Bismuth on the Kidneys of Animals, Judged by the Non-protein Nitrogen and Urea Content of the Blood, Arch. Dermat. & Syph. **10**:1-13 (July) 1924.

amount of bismuth salt circulating in the blood stream might have been sufficient to cause the toxemia. On the other hand, the volume of bismuth solution, from 7 to 10 cc., that entered the ureter and renal pelvis in the second case seems too small to have been the sole cause of the toxic effects. The possible presence, however, of more highly toxic bismuth compounds in the solution must be duly considered.[10] Another factor to be reckoned with was the presence of renal changes, which might have allowed greater absorption and systemic circulation of the toxic compound, resulting in general toxemia. The data in the present study do not warrant a definite conclusion as to whether the toxemia was due to the bismuth salt itself or to more highly toxic bismuth compounds acting on pathologic renal tissue. A combination of these factors seems most probable.

COMMENT

Twenty-five years ago poisoning due to bismuth subnitrate occurred not infrequently.[11] This substance, a medium opaque to roentgen rays, was employed as a diagnostic aid in investigating suspected lesions in the gastro-intestinal tract; it was used also in dusting powders and pastes, as for example in paste of bismuth N. F., to secure the healing of wounds and infected sinus tracts.[12] With the development of toxemia, cyanosis due to methemoglobinemia was often present.[13] Since one of us,[14] while investigating the diuretic properties of ammonium nitrate in 1928, observed transient methemoglobinemia in two cases, without alarming or uncomfortable symptoms, and rapid disappearance of the cyanosis when the administration of the salt was discontinued, we have been of the opinion that the serious toxic symptoms of bismuth subnitrate poisoning have been due to the bismuth rather than to the

10. Leonard, C. S.: Studies in the Pharmacology of Bismuth Salts: II. Toxicity and Urinary Elimination of Soluble Bismuth Salts, J. Pharmacol. & Exper. Therap. **28**:89-108 (July) 1926. Leonard, C. S., and O'Brien, J. L.: Studies in Pharmacology of Bismuth Salts: III. Toxicity and Urinary Elimination of Potassium Bismuth Tartrate, ibid. **28**:109-119 (July) 1926.

11. Cabot, R. C.: Bismuth Poisoning, with Report of a Case, Tr. A. Am. Physicians **27**:457-470, 1912. Mayer, Leo, and Baehr, George: Bismuth Poisoning: A Clinical and Pathological Report, Surg., Gynec. & Obst. **15**:309-322 (Sept.) 1912. Warfield, L. M.: Bismuth Poisoning, Am. J. M. Sc. **144**:647-658 (Nov.) 1912.

12. Higgins, W. H.: Systemic Poisoning with Bismuth, J. A. M. A. **66**:648-650 (Feb. 26) 1916.

13. Phillips, John: Bismuth Poisoning and Nitrate Poisoning from the Use of Bismuth Subnitrate, with Report of Three Cases, Cleveland M. J. **16**:419-428 (June) 1917.

14. Eusterman, G. B., and Keith, N. M.: Transient Methemoglobinemia Following Administration of Ammonium Nitrate, M. Clin. North America **12**:1489-1496 (May) 1929.

nitrate radical. The two present cases, in which toxemia was undoubtedly due to bismuth, lend further support to such an explanation.

The acute onset of oliguria and stomatitis suggests poisoning by a heavy metal. Mercury bichloride is the most common agent causing such a syndrome that one meets clinically. Stomatitis due to bismuth intoxication can be distinguished from that due to mercury compounds by the gradual development of blue-black areas of discoloration on the gums and buccal mucous membrane. It is of interest also to point out that in acute lead poisoning, which one might consider if confronted with the symptoms observed in bismuth intoxication, renal insufficiency does not occur.[15] This absence of renal damage in acute intoxication due to lead was strikingly apparent to a group of those in the clinic administering lead compounds therapeutically in cases of various types of advanced malignant growths. In concluding this report we wish to stress the importance of considering bismuth intoxication as a possible etiologic factor whenever there are rapidly developing oliguria and stomatitis.

15. Horton, B. T.; Bargen, J. A., and Osterberg, A. E.: Personal communication to the authors.

INHERITANCE OF THE SHAKING PALSY

WILLIAM ALLAN, M.D.
CHARLOTTE, N. C.

Shaking palsy, first adequately described by Parkinson[1] in 1817 and since generally known as Parkinson's disease, appears mostly in persons in the latter half of life. It is characterized by muscular rigidity and weakness, tremor, a propulsive gait and masklike facies, without disturbances of sensation or reflexes. The most striking symptom, tremor, is characterized by short oscillations of the head or extremities at the rate of from 4 to 7 a second and is most pronounced during rest, as contrasted with the intention tremors of senility and of multiple sclerosis.

According to J. Ramsay Hunt,[2] "Paralysis agitans . . . is not a disease *sui generis* but a syndrome referable to the efferent neurons of the corpus striatum (striatal and pallidal). This syndrome may be produced by a variety of pathologic lesions, viz., primary atrophy, senile degeneration, and vascular, inflammatory and neoplastic lesions. Therefore, primary and secondary forms are recognized."

Medical authorities[3] suggest various causes for this syndrome, such as prolonged physical strain, emotion, trauma and exposure to cold, but there is no evidence to show that these factors are important.[4] Heredity is mentioned as a causative factor by some authors and overlooked or denied by others. In investigating the hereditary factor in shaking palsy, manifestly the cases in which it is due to inflammation or to neoplasm need not be considered.

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1. Parkinson, cited by Ostheimer, A. J.: An Essay on the Shaking Palsy, by James Parkinson, M.D., Member of the Royal College of Surgeons, Arch. Neurol. & Psychiat. **7**:681 (June) 1922.

2. Hunt, J. Ramsay: Primary Paralysis Agitans, Arch. Neurol. & Psychiat. **30**:1332 (Nov.) 1933.

3. McCarthy, D. J., in Osler, W., and McCrae, T.: Modern Medicine, Philadelphia, Lea & Febiger, 1928, vol. 6, p. 767.

4. Grimberg, L.: Paralysis Agitans and Trauma, J. Nerv. & Ment. Dis. **79**:14 (Jan.) 1934.

Gowers and Berger each found a family history for 15 per cent of their patients,[3] and Patrick and Levy [5] found evidence of direct inheritance for 6 of 146 patients. Bell and Clark,[6] in 1926, reported a pedigree and gathered reports of 9 other families from the literature. These 10 pedigrees, with 1 published by Kückens,[7] constitute all the data so far published on which to base an opinion as to the inheritance of shaking palsy. Two of these pedigrees showed palsy in 1 parent and 1 or 2 children; 3 showed it in a single fraternity, and 1 showed it in 7 of 9 sibs, with 3 instances in the second generation. Kückens' pedigree embraced three generations, and there were 3 pedigrees running through three or four generations that were indicative of a dominant trait, but the pedigree published by Lundborg, embracing three generations, suggested a recessive trait.[8]

Because of the paucity and conflicting nature of this evidence, I have examined 72 consecutive patients with the parkinsonian syndrome from whom it was possible to secure an adequate family history. In 7 cases there was no family history of this disorder but a past history of probable encephalitis; in 20 cases neither the family nor the past history offered an explanation of the syndrome; in 45 cases near relatives, parents, siblings or children, had the same disorder. For only 24 of the 45 patients with a history of palsy was the family history complete, and the charts showing these pedigrees are reproduced here (charts 1 to 24).

A summary of the data presented in these pedigrees shows a sex ratio of 3 men to 2 women (153 to 105), which is the same ratio reported by Patrick and Levy. There are several instances in which both men and women have been married twice to partners without palsy and have passed the trait on to both sets of children. The preponderance of men is not due to sex linkage but is possibly caused by some environmental factor.

There are 79 instances in which the trait was present in the children and in 1 parent (father, 43; mother, 36). The appearance of

5. Patrick, H. T., and Levy, D. M.: Parkinson's Disease, Arch. Neurol. & Psychiat. **7**:711 (June) 1922.

6. Bell, Julia, and Clark, A. J.: A Pedigree of Paralysis Agitans, Ann. Eugenics **1**:455 (April) 1926.

7. Kückens, H.: Ueber Heredofamiliarität bei Paralysis agitans; zugleich ein Beitrag zum hereditär bedingten Auftreten des Diabetes mellitus bei eineiigen Zwillingen, Klin. Wchnschr. **4**:2289 (Nov. 26) 1925.

8. Baur, E.; Fischer, E., and Lenz, F.: Human Heredity, New York, The Macmillan Company, 1931, p. 417.

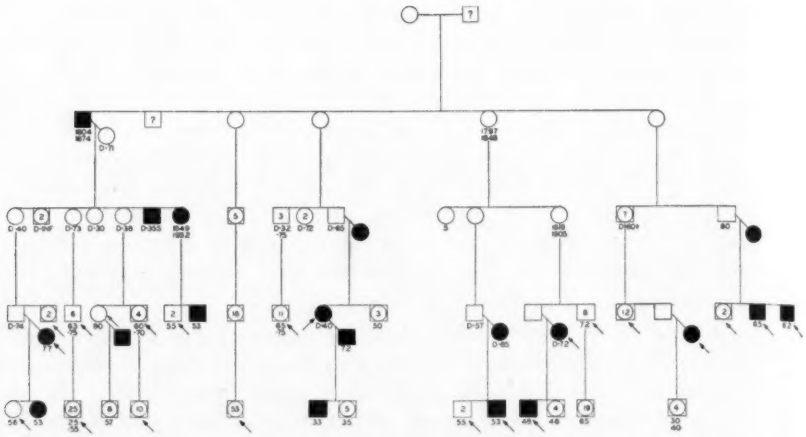


Chart 1.—In charts 1 to 24 a square indicates a male; a circle, a female, and a square and circle combined, both sexes. A black square or circle indicates palsy; and a question mark, status with regard to palsy not known. A number within a square, circle or combined square and circle indicates the total number of children represented; a number appearing below a square or circle, the age; *D* followed by a number, the age at time of death; *D—Inf* died in infancy; *S* single; arrows, the members whom I have seen.

McD. (I, 2) emigrated from Scotland and settled in Mecklenburg County, N. C., about the time of the Revolutionary War. By his first marriage he had 2 sons and 4 daughters. One son, the second member of the second generation (II, 2), moved across the mountains to Tennessee and was lost track of; the other son (II, 1) died at the age of 71 and is reported by many of his grandchildren to have had shaking palsy severely. None of the grandchildren and great grandchildren of McD.'s 4 daughters by this marriage have had palsy unless it was introduced into the family by marriage. The first son in generation II (II, 1) had 8 children, 2 (III, 2) dying in infancy and 3 married daughters dying before the age of 40 (III, 1, 4 and 5). One of these daughters died childless; the other 2 left 8 children, 4 of whom, all over 65, I examined and found without tremor. A fourth daughter of II, 1 lived to be over 70. She left 6 children who lived to be over 63, 2 of whom I have seen. There is no palsy in the descendants of these daughters. III, 6, the son of II, 1 showed palsy early and died a bachelor at the age of 35. The sixth daughter (III, 7) died at the age of 83 with palsy, and 1 of her 3 sons (IV, 7), aged 53, has palsy. In generation III there were 2 men who married wives with palsy (half first cousins), and the trait appeared in their children (IV, 10, 18 and 19). Six members of generation IV married partners with palsy (cousins in 5 instances), and palsy has appeared in the children of 4 of these couples. The oldest children of the other 2 couples are 57 and 40 years old, respectively (V, 4 and 14).

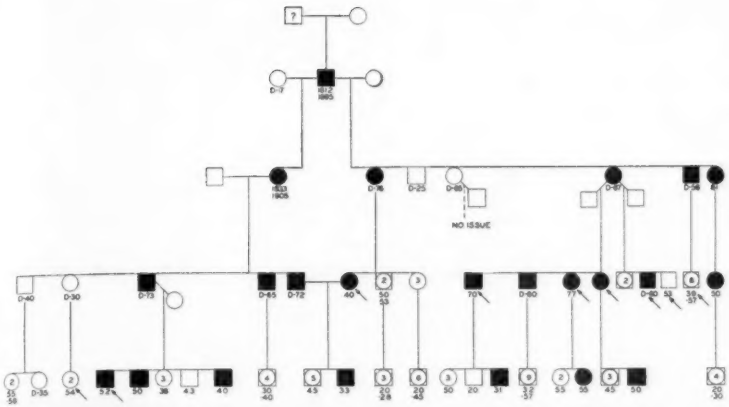


Chart 2.—McD.'s second marriage resulted in 1 son (II, 2), who died at the age of 83 with palsy, as reported by several of his grandchildren. This son married four times, raising 2 sets of children. By his first wife there was 1 daughter (III, 2) who died at the age of 72 with palsy. She left 5 children (IV, 1 to 5). Two of these children died when 30 and 40 years old, respectively, and none of their children (V, 1 to 3), the oldest being 58, have as yet shown any tremor. III, 2's other 3 children (IV, 3 to 5) all had palsy, and the malady has reappeared in the children (V, 4, 5, 8 and 11) of 2 (IV, 3 and 5). The children of the third son (IV, 4) are still under 40. McD's son's second marriage resulted in 6 children, 1 of whom died young and unmarried, 4 had palsy and 1 did not. One of the palsied daughters (III, 3) has passed the trait to 1 of 3 children reaching the age of 50; another (III, 6) has raised 2 sets of children, and palsy has appeared in both sets (IV, 9 to 12 and 14); a third child with palsy (III, 7) had 8 children, the oldest now 57, but so far none is palsied. The fourth child with palsy (III, 8) passed it to her only child (IV, 17). IV, 10 left 9 children, the oldest now 57, none of whom is palsied. The 42 affected members of this family are about equally divided as to sex, 24 men and 18 women. The trait has descended through both men (4) and women (12) and has appeared in both sets of children when both an affected mother and an affected father have married twice.

The collateral descendants of both of McD.'s wives and both of the wives of his son by his second marriage live in Mecklenburg County, N. C., and do not have palsy.

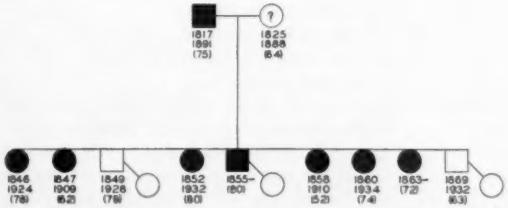


Chart 3.—This is the only family that has refused to cooperate; information had to be obtained from friends and the family physician. The father and 7 of 9 children were palsied; 6 of them never married.

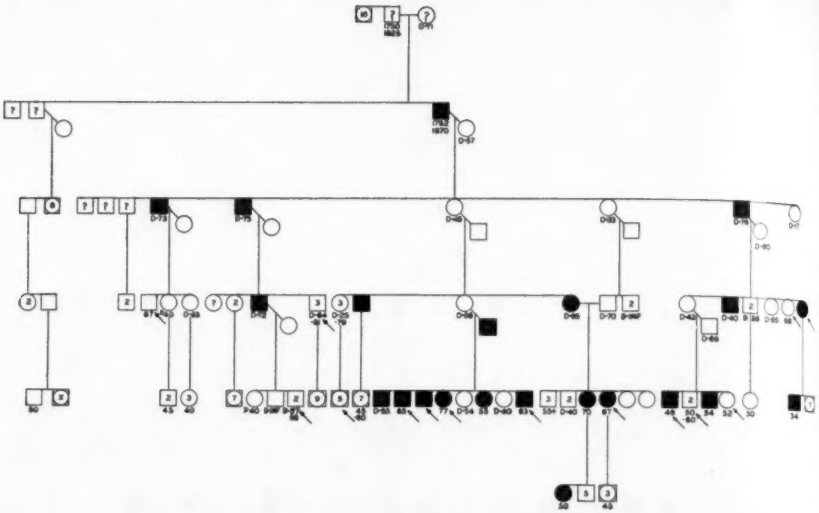
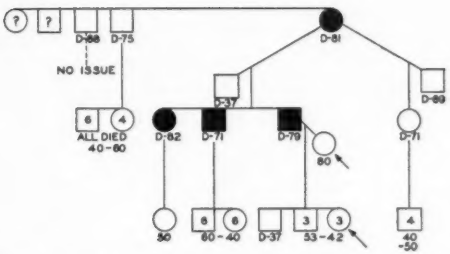


Chart 4.—The ancestor of this family (I, 2) moved from Augusta County, Va., to Mecklenburg County, N. C., before the Revolutionary War and died in 1825. There is no memory of him among his descendants. There were 3 sons, James (II, 1), of whom there is no record; John (II, 2), whose grandchildren have no palsy, and William (III, 3), 1782-1870, whose grandchildren report that 1 slave's sole duty was to feed and care for the palsied old man. William left 9 children; 3 sons (III, 3 to 5) moved to Tennessee, and nothing further is known about them. Of the 6 children remaining in North Carolina, the 3 sons all lived to be over 73, and all had shaking palsy. The oldest son (III, 6) had 3 children, a son (IV, 4), now 67, without palsy and childless, and 2 daughters (IV, 5 and 6), who died at 40 and 63 years of age, without palsy. The grandchildren are not over 45. The fifth son (III, 7) of II, 3 left 7 children, 1 of whom I interviewed when he was aged 81. One daughter (IV, 7) moved west, and only 1 (IV, 9) of the 6 remaining children is reported to have had palsy. IV, 9 left 4 children, 2 of whom died before reaching 40, 1 died while under my care when he was 57, without palsy, and the other writes me that he has no sign of palsy at the age of 68. II, 3's oldest daughter (III, 8) died in 1860, when 45 years old. She was too young to show palsy; but as 2 of her children (IV, 12 and 14) had palsy, she doubtless transmitted the trait. The oldest daughter (IV, 11) of III, 8 died when 79 and left 2 sons, now 58 and 56, all without palsy. III, 8's oldest son had palsy, but none of his 7 children, the oldest being 60 has it so far. Two of III, 8's daughters (IV, 11) died young without palsy, 1 leaving 2 sons, who died young and unmarried, and the other leaving 1 daughter, who died when 69 without palsy. III, 8's fourth daughter (IV, 13) died when 56 without palsy; she had married a man in whom palsy developed and left 8 children (V, 12 to 19) 6 of whom, above the age of 55, have palsy. Two children died at the age of 40 and 54, respectively, without showing palsy. Because so many of these children have palsy, it seems likely that IV, 13 carried the trait. III, 8's youngest daughter (IV, 14) died at the age of 85 with palsy, and of her 9 children, 2 died before reaching 40, 2 have palsy and 5 have no palsy as yet. III, 9 died at the age of 33 without palsy, leaving 3 children (IV, 15 and 16), of whom 2 died young and childless without palsy and 1 died at the age of 70 without palsy. III, 10 died at the age of 78 with palsy, leaving 7 children. The oldest child (IV, 17) died at the age of 43 without palsy; but as 2 of her 5 children already show palsy and there is no sign of palsy in her husband's family, it seems reasonable to assume that she carried the trait. The second child (IV, 18) of III, 10 died childless at the age of 40 with palsy. A third child died childless when 38 without palsy, and a fourth (IV, 19) died when 40 without palsy, leaving 1 daughter, who does not show signs of palsy at the age of 50. Two of III, 10's single daughters (IV, 20 and 21) passed the age of 65 without palsy, but her youngest daughter (IV, 22) has palsy at the age of 65, and 1 of the latter's children has it. In the seventh generation there is 1 instance of palsy in a person aged 50. X for V, 2 indicates number of children unknown.



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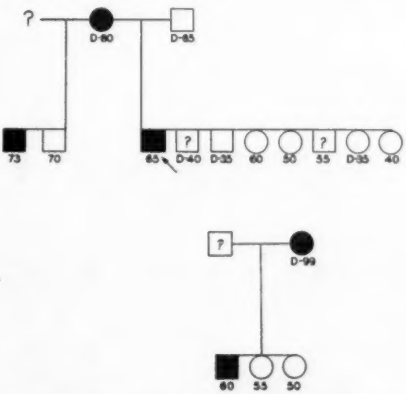

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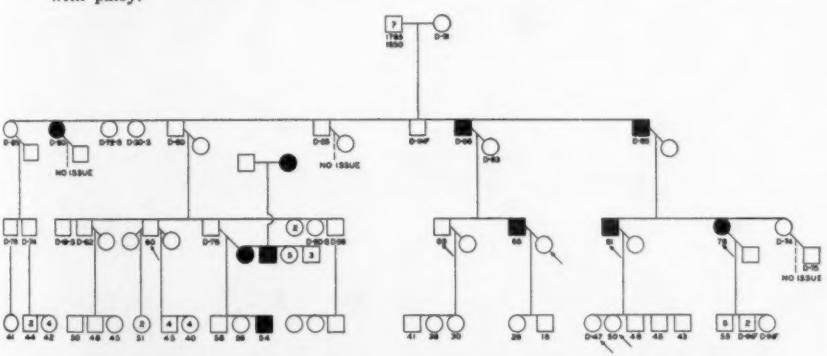

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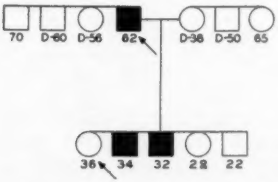

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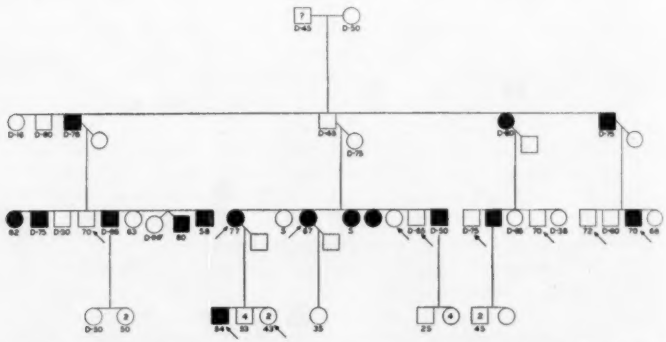

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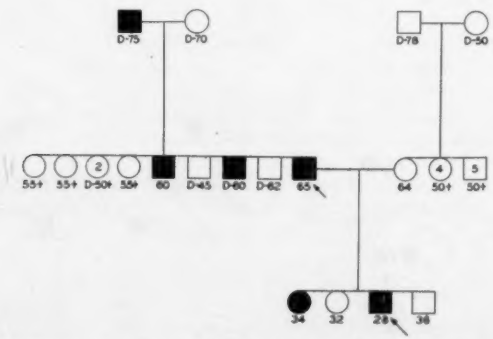

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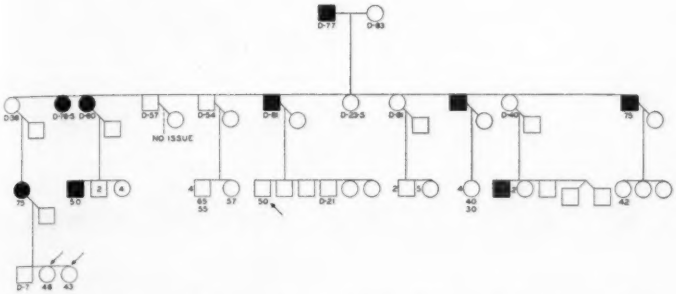

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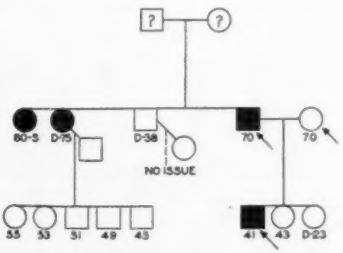

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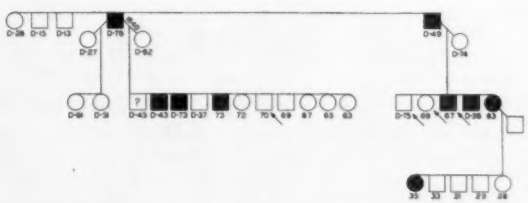

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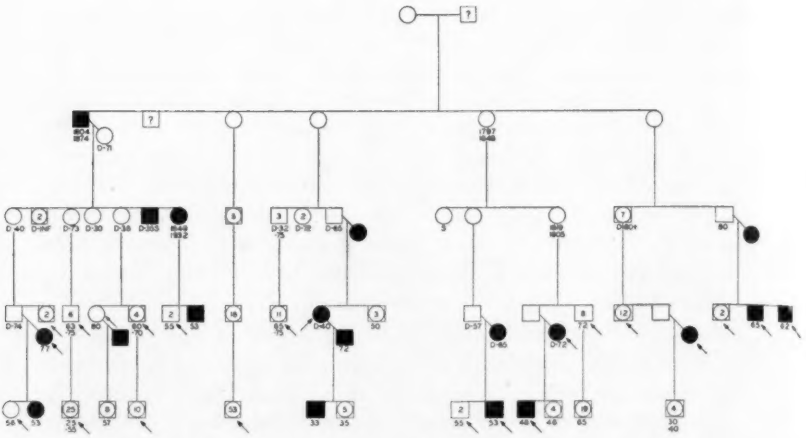


Chart 1.—In charts 1 to 24 a square indicates a male; a circle, a female, and a square and circle combined, both sexes. A black square or circle indicates palsy; and a question mark, status with regard to palsy not known. A number within a square, circle or combined square and circle indicates the total number of children represented; a number appearing below a square or circle, the age; *D* followed by a number, the age at time of death; *D—Inf* died in infancy; *S* single; arrows, the members whom I have seen.

McD. (I, 2) emigrated from Scotland and settled in Mecklenburg County, N. C., about the time of the Revolutionary War. By his first marriage he had 2 sons and 4 daughters. One son, the second member of the second generation (II, 2), moved across the mountains to Tennessee and was lost track of; the other son (II, 1) died at the age of 71 and is reported by many of his grandchildren to have had shaking palsy severely. None of the grandchildren and great grandchildren of McD.'s 4 daughters by this marriage have had palsy unless it was introduced into the family by marriage. The first son in generation II (II, 1) had 8 children, 2 (III, 2) dying in infancy and 3 married daughters dying before the age of 40 (III, 1, 4 and 5). One of these daughters died childless; the other 2 left 8 children, 4 of whom, all over 65, I examined and found without tremor. A fourth daughter of II, 1 lived to be over 70. She left 6 children who lived to be over 63, 2 of whom I have seen. There is no palsy in the descendants of these daughters. III, 6, the son of II, 1 showed palsy early and died a bachelor at the age of 35. The sixth daughter (III, 7) died at the age of 83 with palsy, and 1 of her 3 sons (IV, 7), aged 53, has palsy. In generation III there were 2 men who married wives with palsy (half first cousins), and the trait appeared in their children (IV, 10, 18 and 19). Six members of generation IV married partners with palsy (cousins in 5 instances), and palsy has appeared in the children of 4 of these couples. The oldest children of the other 2 couples are 57 and 40 years old, respectively (V, 4 and 14).

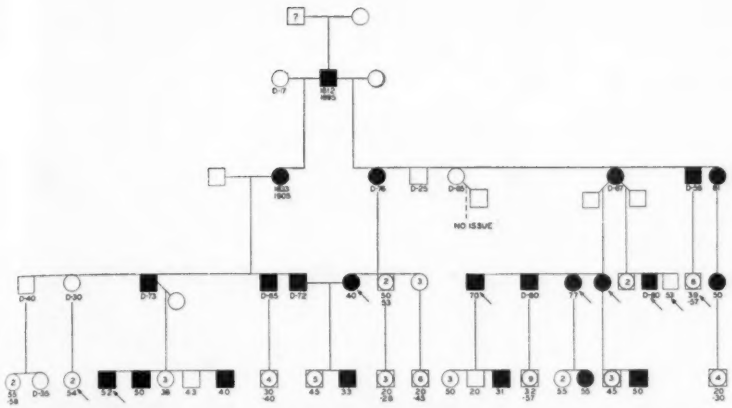
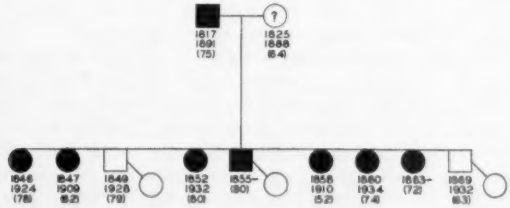


Chart 2.—McD.'s second marriage resulted in 1 son (II, 2), who died at the age of 83 with palsy, as reported by several of his grandchildren. This son married four times, raising 2 sets of children. By his first wife there was 1 daughter (III, 2) who died at the age of 72 with palsy. She left 5 children (IV, 1 to 5). Two of these children died when 30 and 40 years old, respectively, and none of their children (V, 1 to 3), the oldest being 58, have as yet shown any tremor. III, 2's other 3 children (IV, 3 to 5) all had palsy, and the malady has reappeared in the children (V, 4, 5, 8 and 11) of 2 (IV, 3 and 5). The children of the third son (IV, 4) are still under 40. McD's son's second marriage resulted in 6 children, 1 of whom died young and unmarried, 4 had palsy and 1 did not. One of the palsied daughters (III, 3) has passed the trait to 1 of 3 children reaching the age of 50; another (III, 6) has raised 2 sets of children, and palsy has appeared in both sets (IV, 9 to 12 and 14); a third child with palsy (III, 7) had 8 children, the oldest now 57, but so far none is palsied. The fourth child with palsy (III, 8) passed it to her only child (IV, 17). IV, 10 left 9 children, the oldest now 57, none of whom is palsied. The 42 affected members of this family are about equally divided as to sex, 24 men and 18 women. The trait has descended through both men (4) and women (12) and has appeared in both sets of children when both an affected mother and an affected father have married twice.

The collateral descendants of both of McD.'s wives and both of the wives of his son by his second marriage live in Mecklenburg County, N. C., and do not have palsy.



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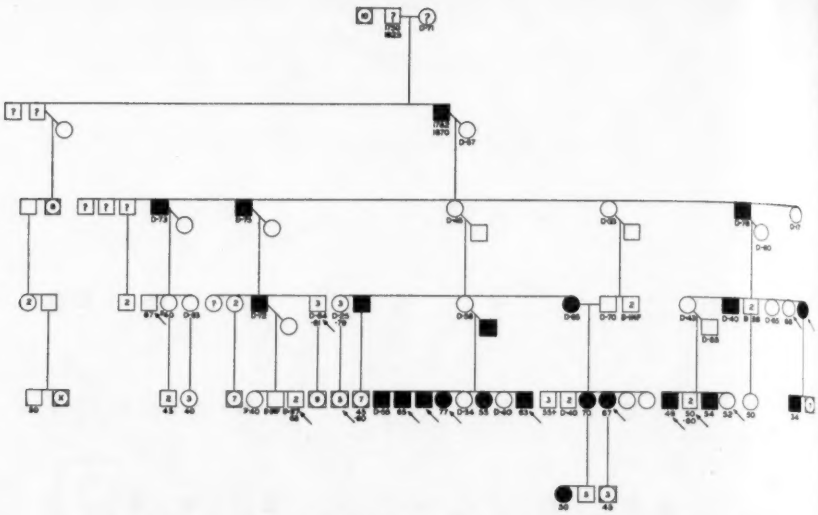

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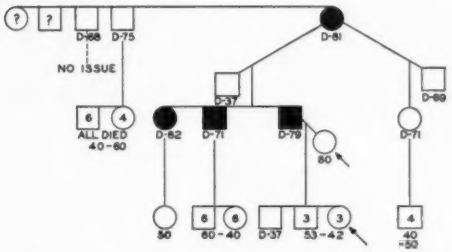

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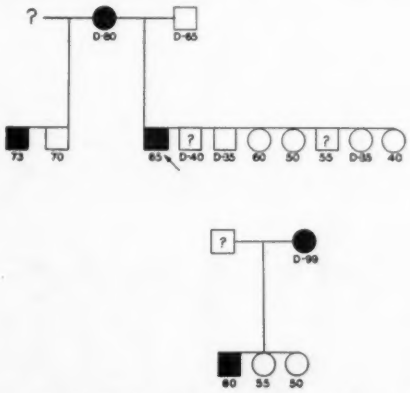

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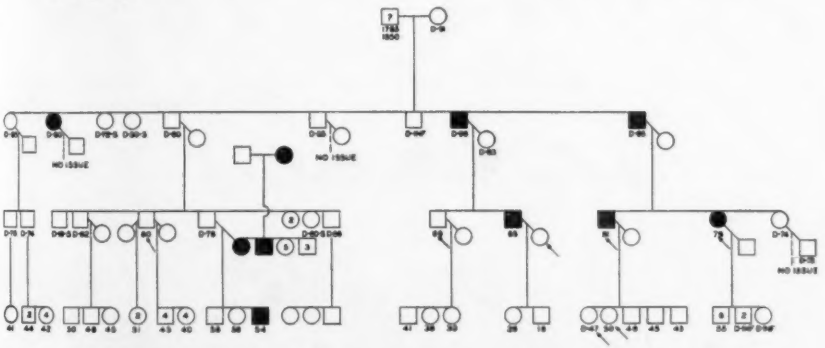

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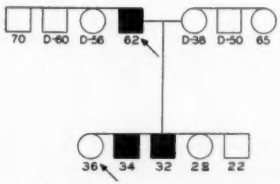

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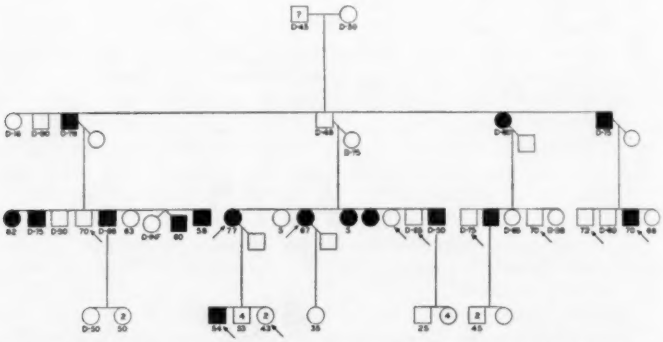

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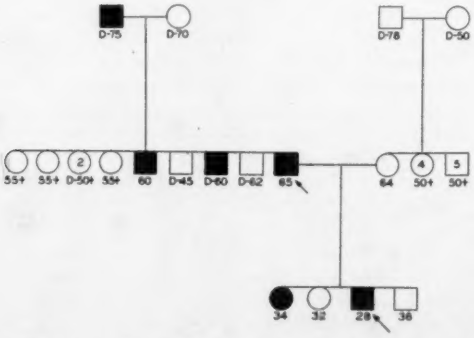

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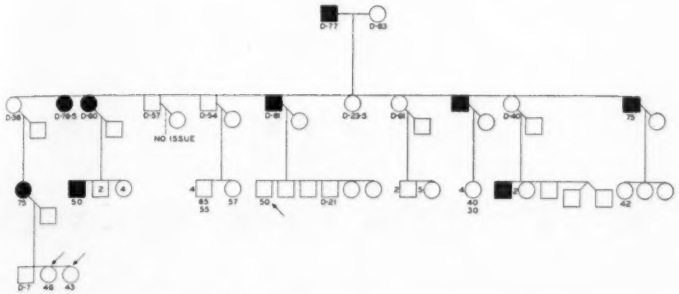

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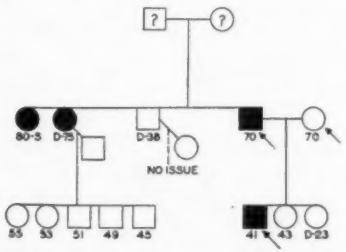

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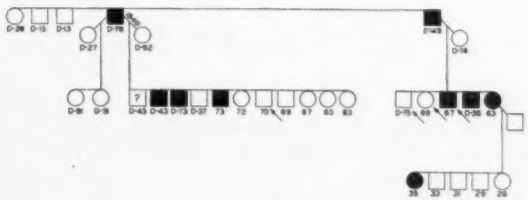

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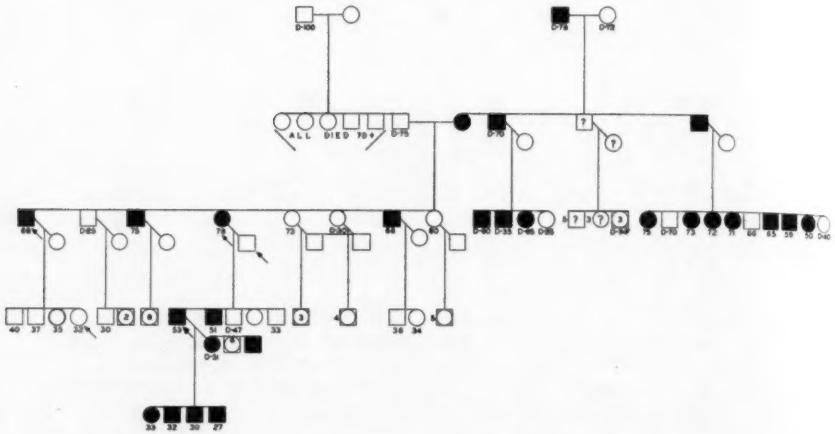
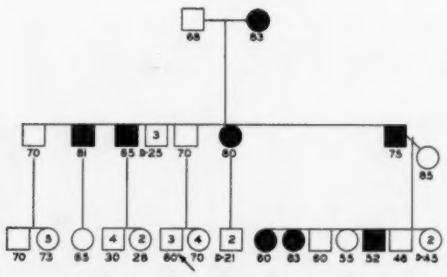


Chart 14.—I spent a day with Dr. J. Q. Myers traveling over the mountains of Wilkes County, interviewing various members of this family. I was unable to see the 4 children of IV, 8, but he assured me that all of them have the same tremor he has, which is marked.



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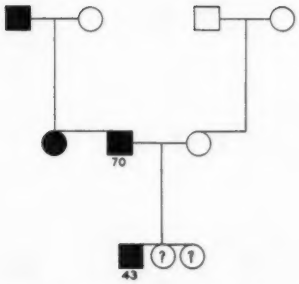

Chart 16.—This pedigree was sent to me by Dr. Tilman Ramsey, of Kentucky, and I cannot enlarge on it.

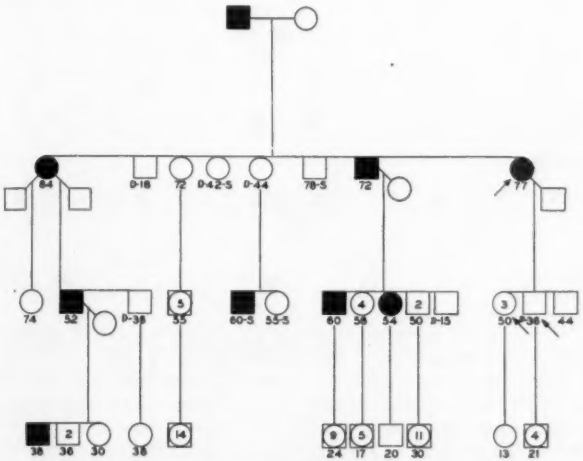

Chart 17.—The pedigree of this Burke County family, coming originally from Powhatan County, Va., was supplied by II, 8, who has been a patient of mine for a number of years. Since the son of II, 5, has palsy, I judge his mother, who died when 44, carried the trait.

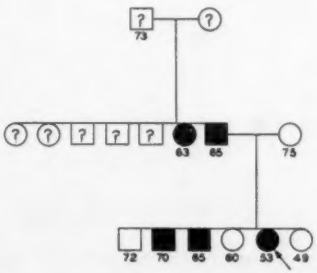

Chart 18.—This pedigree of a South Carolina family was supplied by III, 5, who knew little about her father's sibs and parents.

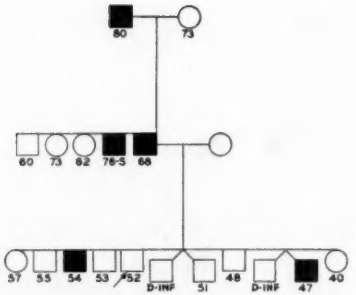

Chart 19.—This pedigree was furnished by III, 5, and by Dr. John I. Barron, of York, S. C.

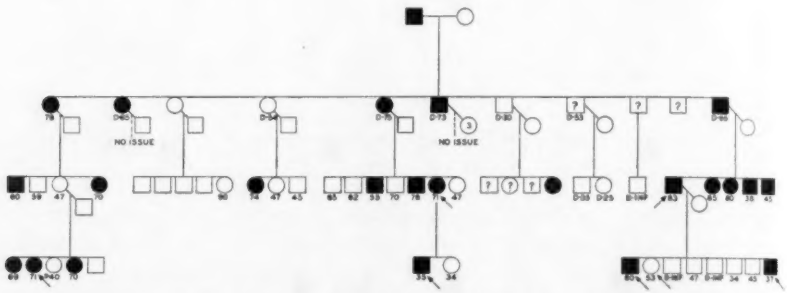

Chart 20.—I became interested in this family when I saw III, 27, in an elevator in a hospital. The old gentleman was covered up to the neck with a sheet, but his long white beard on a severely palsied chin could have flagged down an express train. I made several trips to Anson County to visit his relatives and to ask again about his sibs who live in Arkansas and Texas. He insists they all have palsy (III, 28 to 31) but the accuracy of this seems doubtful. Two members of the second generation (II, 4 and 7) of this family have been considered to be carriers.

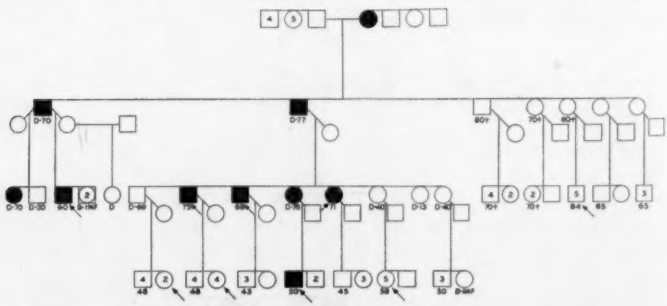

Chart 21.—Some of the members of this family are neighbors of mine, and I saw the 4 living members of the third generation who have palsy as well as most of the next generation at a family reunion in 1935.

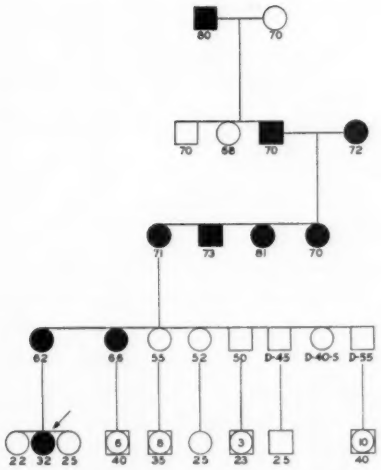

Chart 22.—V, 2 was sent to me because of marked shaking palsy. With the help of her mother she worked out the pedigree of this Georgia family.

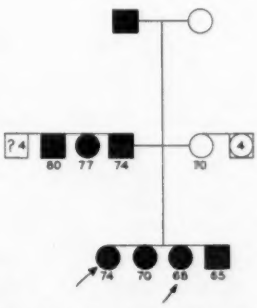

Chart 23.—This pedigree of a South Carolina family was given to me by III, 1. As usual, pedigrees supplied by a single member of a family are not extensive.

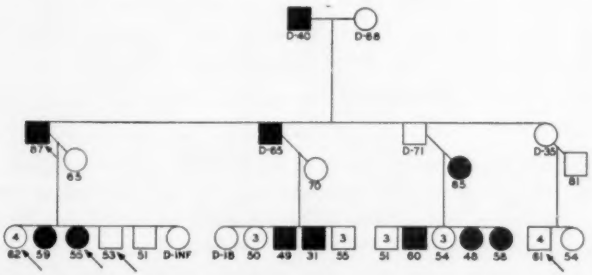

Chart 24.—This pedigree of a Mecklenburg County family was supplied by II, 1 and his children. I have seen palsy in members of other branches of this large clan.

shaking palsy in any person depends largely on age, as demonstrated by Patrick and Levy's table showing the time of onset.

Age, Years	Percentage
21-30	3.4
31-40	13.7
41-50	28.0
	45.1
51-60	33.6
61-70	18.6
71-80	2.7
	100.0

Bell and Clark in a compilation of 423 cases found the average age of onset to be 52.4 years. One half (146) of the 290 children of 79 parents who lived to be over 50 had palsy.

In 36 instances palsy was present in a parent but not in the children. In 28 of these families the children were under 50 years of age; in the remaining 8 families only 15 of the 47 children had reached the age of 50.

In 8 instances there was skipping of a generation; 6 of the parents were under 50, 1 was 54 and 1 was 56.

Six whole sibships were reported as having palsy; 1 of these fraternities lives in North Carolina, but the members of the other 5 are scattered from Arkansas to Kentucky, and the history could not be verified by examination. In 2 other families a similar history was found to be incorrect when all the members of the fraternities were examined; so such a history is of doubtful accuracy.

In three instances both parents were reported as having palsy; in 1 instance there were 6 children under 40, with 1 affected; in 1 all 4 children lived to be over 70 and were affected (Georgia); in 1 all 4 children, aged 27 to 33, were said by the father to be affected.

The majority of these pedigrees could be greatly enlarged were sufficient time and effort applied to the task. However, the material that has been gathered in the course of daily practice and presented here demonstrates beyond doubt the important rôle played by heredity in the incidence of shaking palsy.

CONCLUSION

Although the occasional failure of shaking palsy to appear in the children of palsied parents and the skipping of generations, with the history of entire fraternities being affected, suggest recessiveness of this trait, the greater weight of the evidence indicates that in about two thirds of the cases studied in North Carolina shaking palsy was inherited as a dominant trait, probably conditioned by a single autosomal gene.

PULSATIONS OF THE WALL OF THE CHEST

II. PULSATIONS ASSOCIATED WITH AORTIC REGURGITATION

WILHELM DRESSLER, M.D.
VIENNA, AUSTRIA

In the presence of aortic regurgitation the left ventricle is dilated and does an increased amount of work. This leads to the formation of a strong cardiac thrust, which may range from a circumscribed increased apical thrust to a diffuse bulge of the precordium. The formation of this bulge is not rarely interfered with by the effect of systolic aspiration (regarding the reduction of the ventricular volume during the systolic efflux), which may reach a marked degree with this type of valvular lesion. An abnormally large quantity of blood flows during systole from the dilated left ventricle into the arteries, and the bulk of it leaves the thorax, resulting in a rapid fall in intrathoracic pressure. So far as this condition is not compensated for by the inspiratory movement of the column of air within the lungs, two means of compensation are available: first, by an increased aspiration of venous blood into the chest and, second, by a reduction of the intrathoracic space, i. e., by a flattening of the ventral wall. A diffuse depression of the ventral wall of the chest is therefore not rarely encountered in the presence of aortic regurgitation; this was first described by Lang [1] and later by Ortner,[2] and personal investigations led to the same findings in not a few cases.[3] This pulsatory phenomenon, however, is not a constant finding. Occasionally it is missed entirely, and if present, there is considerable variation as to extent and degree of depression of the thoracic wall. The varying appearance of pulsations in aortic regurgitation depends on several factors, the causal interplay of which may not always be clear in a given case.

The intensity of pulsations over the heart as well as over the hepatic area depends on the degree of the valvular lesion, and that means on the amount of blood which during systole disappears from the thoracic cavity and on the abruptness of the fall in pressure. The faster the

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Translated by Hugo Roesler, M.D., Philadelphia.

From the *Herzstation*, Dr. Hans Horst Meyer and Dr. Emil Zak, directors.

1. Lang, G.: Ueber einige durch die Herzaktion verursachte Bewegungen der Brustwand und des Epigastriums, Deutsches Arch. f. klin. Med. **108**:35, 1912.

2. Ortner, N.: Physikalische Erscheinungen in der Präcordialgegend und deren Deutung, Med. Klin. **25**:63, 1929.

3. Dressler, W.: Die Brustwandpulsationen als Symptome von Herz und Gefässkrankheiten, Vienna, Wilhelm Maudrich, 1933.

blood leaves the thoracic cavity, the less closely will the inspiration of air into the lungs and the relatively slow influx of venous blood keep pace with it, and the more strongly will aspiration act on the wall of the chest. In addition, varying conditions of the lungs, their capacity for expansion and the elasticity of the bony skeleton will influence the formation of the pulsatory picture.

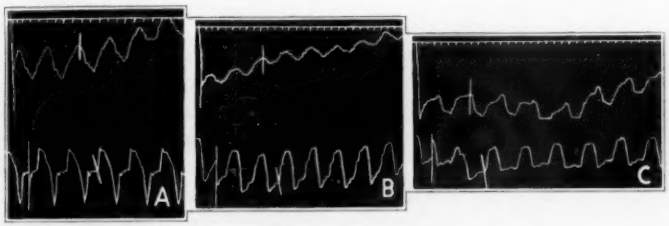
The effect of systolic aspiration of the thoracic wall is often partly or completely neutralized by the opposing force of the systolic change in shape of the heart, as expressed, for instance, by the more forceful cardiac thrust. One therefore finds in certain cases of aortic regurgitation a diffuse propulsion of the precordial area instead of a systolic depression. One often finds a well marked systolic depression mesiad to the forceful apical thrust; this leads to a peculiar seesaw movement. It must be emphasized that the systolic depression affects several intercostal spaces and extends in instances of high grade valvular defect far beyond the cardiac area, over the whole left side of the chest and at the right to the parasternal line. This diffuse depression must not be confused with the localized systolic depression which is commonly noted in the immediate vicinity of a forceful apical thrust. I assume, in accord with Mosso, that the propulsion of the thoracic wall due to the impact of the left ventricle is of significance for the development of the diffuse depression, in addition to the marked systole. This concept is supported by the fact that the graph of the movement of the thoracic wall shows a definite dip at the very beginning of the systole during the isometric period, hence at a time at which the systolic aspiratory effect could not play a rôle.

The systolic depression of the thoracic wall is followed by a ventral diastolic movement, which is rather slow, in contrast to the condition in certain cases of adhesive pericardial disease and tricuspid regurgitation, in which the systolic depression is followed by a jerky rebound of the thoracic wall. Lang has pointed out that in the latter conditions a forceful apical thrust is absent and that therefore the centripetal systolic as well as the centrifugal diastolic forces act without inhibition, whereas in aortic regurgitation, subsequent to the forceful systolic apical thrust, there results a diastolic centripetal movement of the wall which interferes with the predominant centrifugal impulses.

Ortner likewise has directed attention to the diffuse systolic depression in aortic regurgitation and has stated that this finding is noted only in cases of valvular lesions of endocarditic origin, while it is missing in cases of regurgitation of syphilitic etiology. I cannot subscribe to this statement, because my colleagues and I have found the systolic depression of the ventral wall of the chest in not a few cases of syphilitic aortic regurgitation, and the depression was not less marked

than that observed in cases in which there was a rheumatic etiology. The following case may serve as an example:

R. J., a man aged 61, had syphilitic aortic regurgitation with considerable limitation of physical capacity. Examination revealed that the cardiac area bulged definitely. The apical thrust, which was noted in the sixth intercostal space, 1 inch (2.5 cm.) outside the left midclavicular line, was widened and heaving. The adjacent portions of the sixth and seventh ribs showed extensive movement. Marked systolic depression was noted mesiad to the apical thrust, affecting both soft tissues and ribs. Cephalad it reached to the third rib and caudad to the costal arch; it was more marked at the level of the fourth and fifth ribs (fig. *A*). This depression was still felt over the sternum (figs. *B* and *C*) and over the parasternal portions at the right. The intensity diminished toward the left midclavicular line, owing to the counteracting effect of the systolic lift of the apical thrust. The epigastrium likewise was drawn in during systole. A definite seesaw movement could be felt by palpating the apical thrust with the right hand and placing the left hand with slight pressure over the precordium near the left sternal border. Percussion revealed that the area of cardiac dulness slightly exceeded the right sternal border. The lower sternal area did not reveal an increased flatness. The



The graph demonstrates the systolic depression of the precordium in a case of aortic regurgitation. The lower graph (in all the tracings) shows the apical thrust. The upper graphs were made with the receiver over, *A*, the left parasternal line in the fourth intercostal space, *B*, over the upper portion of the sternum and, *C*, over the lower portion of the sternum.

waist of the heart was present in the second and third intercostal spaces on the left. Auscultation revealed that in the second intercostal space to the right of the sternum there was a short, distinct systolic and a long, peculiarly purring diastolic murmur with musical pitch. A short systolic murmur was heard better over the apical area than at the base, and the diastolic murmur was less rough than the one heard over the upper portions of the chest. The heart rate was 84; there was sinus rhythm, with many premature beats. The blood pressure was 150 systolic and 50 diastolic. The liver was not enlarged. There was no edema. The Wassermann reaction was positive. Roentgenograms showed marked enlargement of the heart, with an oblique diameter of 18 cm. There was dilatation of the aortic loop.

The considerable increase in stroke volume and associated with it the powerful aspiration of venous blood during systole produce characteristic phenomena in the venous pulse. Usually in cases of aortic regurgitation there is a well marked systolic collapse of the jugular

veins. Also the abrupt emptying of the hepatic veins and the accompanying reduction in the volume of the liver occasionally produce a distinct systolic depression of the adjacent thoracic wall. If when palpating the liver one feels a jerky systolic depression of ribs and soft tissues, more easily recognized when the patient is holding his breath, one is justified in suspecting the presence of aortic regurgitation.

Ortner has pointed out that the systolic depression of the thoracic wall, provided it has existed at all, will disappear when cardiac failure with congestion sets in. This is due to the inadequate ventricular systole, whereby the aspiratory effect on the thoracic wall as well as on the column of venous blood is diminished, resulting in diminution or disappearance of the systolic collapse of the liver. A similar effect is noted with the appearance of auricular fibrillation. Occasionally a change in the type of hepatic pulsations is noted in the same patient, depending on compensation or failure and also on disturbances in the cardiac rhythm.

SUMMARY

A diffuse systolic depression of the anterior wall of the chest is found in instances of aortic regurgitation. This is a result of the increased stroke volume of the left ventricle, unless the aspiratory effect, owing to reduction of the ventricular volume during the systolic efflux, is neutralized by the opposing forces due to the systolic change in shape of the heart. In other instances there is no movement of the thoracic wall adjacent to the liver, while a distinct systolic depression is noted over the precordium. The diastolic pulsation of the thoracic wall in aortic insufficiency takes place slowly, as contrasted with the speed noted in the majority of cases of adhesive pericardial disease or tricuspid regurgitation in which an abrupt propulsion of the thoracic wall is noted during diastole.

PULSATIONS OF THE WALL OF THE CHEST

III. PULSATIONS ASSOCIATED WITH TRICUSPID REGURGITATION

WILHELM DRESSLER, M.D.

VIENNA, AUSTRIA

The pulsatory features in the presence of tricuspid regurgitation often show a surprising similarity to those accompanying adhesive pericardial disease, and for this reason there is not infrequently confusion as to the proper diagnosis. Sometimes there is a widespread systolic depression of the wall of the chest in cases of tricuspid regurgitation which now and then markedly exceeds the actual cardiac area. The mechanism of this pulsation, as Lang [1] has shown, is essentially different from that of the pulsation noted in cases of adhesive pericardial disease. When there is tricuspid regurgitation, the right ventricle is usually enormously enlarged and is in wide contact with the ventral wall of the chest. During systole the right ventricle empties only a small amount of blood into the pulmonary artery; the larger amount flows in the direction of lesser resistance, i. e., into the right auricle and hence into the large veins, primarily those of the liver. Thus during every systole there is an unusually marked diminution in the size of the right ventricle, recognized fluoroscopically by the wide marginal excursions of the heart, whereby the ventral wall of the chest, the ribs and the soft tissues are drawn inward. Besides this direct suction, there is an indirect aspiratory action on the thoracic wall. The blood discharged from the right ventricle does not remain in the thoracic cavity, as it does under normal conditions, but for the most part reaches the liver. This results in a rapid fall in the intrathoracic pressure and in an aspiratory action on the thoracic wall. The systolic aspiratory action on the thoracic wall is marked in cases of tricuspid regurgitation for the following reason: A rapid compensation for the fall in intrathoracic pressure by influx of venous blood is impossible because of regurgitation into the veins. Hence, the highest degree of systolic depression of the thoracic wall is often observed in association with tricuspid regurgitation. Commonly this depression is most strongly marked on the lateral portion of the left half of the wall, but other more distant portions also are affected by the indirect aspiratory action. The roentgen-

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1. Lang, G.: Ueber einige durch die Herzaktion verursachte Bewegungen der Brustwand und des Epigastriums, Deutsches Arch. f. klin. Med. **108**:35, 1912.

ologic examination reveals an abnormally large amplitude at the left side of the silhouette which is actually formed by the right ventricle.

Furthermore, the characteristic pulsations of the ventral wall of the chest in the presence of tricuspid regurgitation are much influenced by regurgitation of blood into the liver. Most of the blood from the right auricle is diverted to the enlarged right lobe of the liver. Hence the adjacent sections of the thoracic wall are subjected to a strong thrust directed to the right and outward. This pulsation, together with the systolic depression of the left half of the chest, which likewise is chiefly directed to the right, leads to an abrupt systolic shift of the entire chest from left to right. This pulsation is extraordinarily characteristic of tricuspid regurgitation but is strongly marked only in certain cases. Volhard [2] expressed the opinion that the systolic propulsion to the right is occasioned by regurgitation of blood into the right auricle. This concept is incorrect, for careful palpation shows that the most marked expansion of the right wall of the chest does not occur at the level of the right auricle but farther caudad and outward, at the level of the strongly pulsating right lobe of the liver. If one places the right hand over the cardiac area and the left hand over the liver, one "can feel the blood being thrown back and forth between the hands, between the right ventricle and the liver" (Lang). Thus a characteristic seesaw movement results in cases of tricuspid regurgitation; Volhard called attention to this many years ago.

The systolic depression of the left wall of the chest cannot be observed in all cases of tricuspid regurgitation. It is absent whenever the centrifugal forces of the systolic change in shape of the heart are counteracting the aspiratory action due to the systolic diminution in cardiac volume, particularly in cases in which tricuspid regurgitation is associated with mitral stenosis. The depression is most marked when there is myopathy, associated with a higher degree of muscular tricuspid insufficiency, in which the propulsive forces of the systolic change in shape are usually less marked.

The venous blood, which is under high pressure at the beginning of diastole, flows with increased force toward the right side of the heart. It must be remembered that the flow of venous blood, which normally extends throughout almost the entire cardiac cycle, takes place in cases of tricuspid regurgitation only in the diastolic period. This explains the abrupt and unusually great increase in the volume of the right ventricle during diastole. Frequently it causes an equally rapid propulsion of the adjacent thoracic wall. Sometimes it may be referred to as the rapid diastolic propulsion of the thoracic wall, similar

2. Volhard, F.: Ueber Leberpulse und über die Compensation der Klappenfehler, Berl. klin. Wchnschr. **41**:522, 1904.

to that noted in cases of adhesive pericardial disease. As in obliterative pericarditis, there is heard a reduplicated apical second sound, produced by the rapid distention of the right ventricle at the beginning of diastole.

In a patient showing extreme tricuspid regurgitation the Broadbent sign was also observed, i. e., the systolic retraction of the lower ribs on the left dorsal aspect of the thoracic wall. In these cases the pulsation results from the extreme systolic aspiratory action, which cannot be neutralized quickly enough by expansion of the atelectatic left side of the lung. Hence, not only the ventral wall of the chest but also the posterior dorsal portions of the left half of the chest are depressed by the atmospheric pressure. Broadbent's sign cannot, therefore, by any means be regarded as pathognomonic of adhesive pericardial disease. White [3] has stated that he has observed this sign in a patient with a large heart without obliterative pericardial disease. I observed it once in a patient with aneurysmal dilatation of the left auricle in connection with mitral regurgitation.

It is rare to find isolated tricuspid regurgitation of endocarditic origin which presents the aforementioned pulsatory symptoms in such pure form. The characteristic pulsatory phenomena can be best studied in instances of muscular tricuspid insufficiency. In the following case these findings were present to an excessive degree.

H. A. was a man aged 58. In this case the postmortem diagnosis was relative tricuspid insufficiency, with excessive eccentric hypertrophy of the right ventricle. There was marked dilatation of the right ventricle as well as of the right auricle, the latter forming a sac almost the size of a fist. These two chambers formed the ventral wall of the heart, while the entire left ventricle faced the dorsal wall of the chest. The apical portion was formed by the right ventricle. The tricuspid orifice easily permitted the introduction of four fingers. The edge of the internal leaflet was drawn out and rolled in. The valves of all the orifices were without appreciable change. No etiologic factor could be found to explain the anomalous enlargement of the heart. The pericardial cavity was not obliterated.

When the patient was first examined there was marked cyanosis. No clubbing was noted. The legs showed slight edema. The veins of the neck were much enlarged. The external jugular veins were twice the size of a thumb. All other veins as far as visible were markedly dilated. The veins in the neck revealed an excessively marked regurgitation pulse which extended to the lobe of the ear; with each cardiac contraction there was noted not only a diffuse swelling of the neck but also a jerky movement of the head.

The cardiac area bulged but slightly. Inspection showed an abrupt movement of the whole chest from left to right simultaneous with the radial pulse and the ventricular hepatic pulse; it was therefore systolic. Careful observation revealed this pulsatory movement at the level of the shoulders. The pulsations consisted of two components: One was an inward movement (depression) of the inner and

3. White, P. D.: Heart Disease, New York, The Macmillan Company, 1931.

4. The case has been described by Dr. R. Fischer, of the *Herzstation* (Wien. klin. Wchnschr. **41**:657, 1928; **46**:1544, 1933).

particularly of the lateral portion of the left wall of the chest. The other component produced a definite though less prominent protrusion of the right side of the chest (fig. 1). This pulsatory movement was more forceful in the caudal half of the chest, especially caudad to the sixth rib. On the left side the whole anterior and the lateral wall of the chest moved to the right and inward (dorsad) during systole (fig. 2). This pulsation was slight near the clavicles and increased in intensity caudally. It was more marked between the left midclavicular and the anterior axillary line at the level of the sixth to the eighth rib, corresponding approximately to the apical portion of the heart (fig. 3). An apical thrust could not be found (the postmortem examination showed that the apical portion was formed by the right ventricle and corresponded to the level of the upper aspect of the seventh rib, 2 fingerbreadths outside the midclavicular line). As the sternum was approached the component with the dorsal direction (depression) was less and less pronounced and was replaced by a movement which was almost exclusively frontal and directed to the right during systole. Near the left border of the sternum the type of pulsation changed so far as movement was observed, which was characteristic for the right half of the chest and which was directed to the

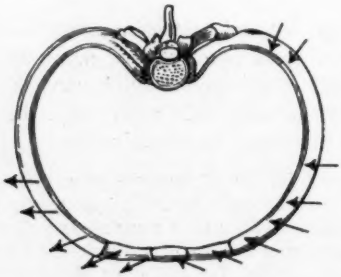

Fig. 1 (patient H. A.).—The arrows indicate the direction of the movements of the thoracic wall observed during systole.

right and outward during systole. On the right side the greatest degree of propulsion was noted over the hepatic area, while from the sixth rib up to the clavicle a similarly directed, though much weaker, pulsatory movement was noted. The lateral borders of the chest on each side revealed a systolic shift to the right, this movement being much more pronounced on the left than on the right. The pulsatory propulsion in the region of the right auricle, i. e., in the parasternal area between the third and the sixth right rib, did not exceed the movements noted over the lateral areas of the same level. When the cardiac area was palpated with the right hand, while the left hand rested over the hepatic area, a definite seesaw movement was felt, with the right hand sinking in during systole and the left hand definitely elevated (fig. 3). The left wall of the chest showed a marked systolic depression and a forceful, almost jerky propulsion at the beginning of diastole. The dorsal aspects of the left wall of the chest below the scapula showed a definite systolic depression which affected the soft tissues as well as the ribs (Broadbent's sign). The liver extended 4 fingerbreadths beyond the costal arch in the right midclavicular line, protruded above the level of the abdomen and revealed an exceedingly forceful systolic pulsation.

Percussion revealed that the cardiac dulness extended 4 fingerbreadths beyond the right sternal border. The lower third of the sternum showed absolute flatness. There was no undue flatness in the second and third intercostal spaces to the left of the sternum and over the upper portion of the sternum.

Auscultation gave surprisingly meager findings. The first sound at the apex was low and not quite pure. The second sound at the apex was definitely reduplicated, with the third accessory sound coinciding exactly with the movement of diastolic propulsion of the thoracic wall. The sounds at the base were hardly audible. No murmur was heard over the lower sternal area, nor was there any sound or murmur to the right of the sternum. The action of the heart was irregular, and auricular fibrillation was evident from the electrocardiogram. The heart rate was 76. The blood pressure was 135 systolic and 80 diastolic.

Roentgenograms revealed marked enlargement of the silhouette on each side, the transverse diameter being 20.5 cm. A wide pulsatory amplitude was noted along the whole left cardiac border, particularly near the base, decreasing in size toward the apical portion. The amplitude on the right was much smaller, and a definite inward movement was noted during systole which was well pronounced

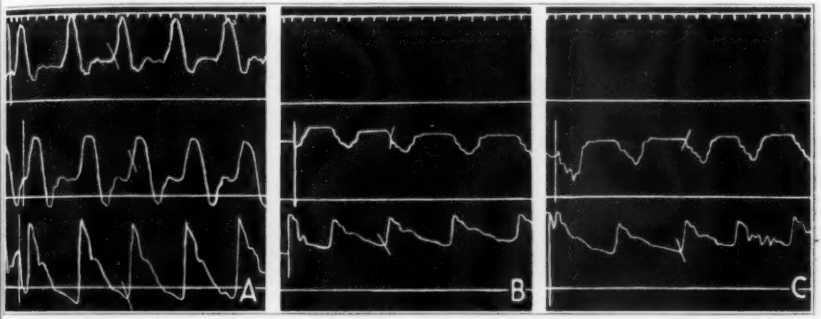

Fig. 2 (patient H. A.).—The graphs demonstrate the systolic depression of the left side of the chest, the venous and hepatic pulse, in the presence of tricuspid regurgitation. *A*, the lower graph is for the radial artery; the middle graph, for the jugular vein, and the upper graph, for the liver. *B*, the lower graph is for the radial artery, and the middle graph, for the left parasternal line at the second intercostal space. *C*, the lower graph is for the radial artery, and the middle graph, for the left parasternal line at the fourth intercostal space.

near the diaphragm. The left leaf of the diaphragm showed a well marked systolic upward shift, while this pulsation was definitely smaller along the right leaf. There was marked dilatation of the superior vena cava, with but small pulsations. The aortic knob revealed a small amplitude; this finding was in marked contrast to the wide amplitude of the left cardiac border, proving that the latter was formed not by the left but by the right ventricle. Oblique views revealed no enlargement of the left auricle. The hilar vessels were not congested; the pulmonary fields showed increased transparency.

The fluoroscopic examination was particularly instructive regarding the pulsations of the thoracic wall. The excessive degree of systolic diminution of the right ventricle which formed the left cardiac contour was expressed by the unusually large amplitude and also by the forceful systolic upward shift (aspiration)

of the left diaphragmatic leaf, while the right diaphragmatic leaf revealed only a systolic upward shift of slight degree. The latter observation is explained by the fact that the right lobe of the liver, which was exceedingly large because of stasis, pulled on the right diaphragm like heavy ballast and prevented it from following the intrathoracic aspiratory force, while the movement of the left diaphragm, inhibited but slightly by the smaller left lobe of the liver, received a forceful pull from the direct aspiration of the caudal cardiac facies.

Isolated or predominant tricuspid regurgitation reveals a diffuse depression of the cardiac area but no apical thrust, provided the apical portion is formed by the enlarged right ventricle. The circumscribed apical thrust due to an increased activity of the left ventricle, in combination with a lesion of the aortic valve or mitral regurgitation, as a rule will be the less marked the more the tricuspid regurgitation prevails. Volhard and Lang accounted for this finding by assuming that the left ventricle is displaced by the enlarged right ventricle. There is

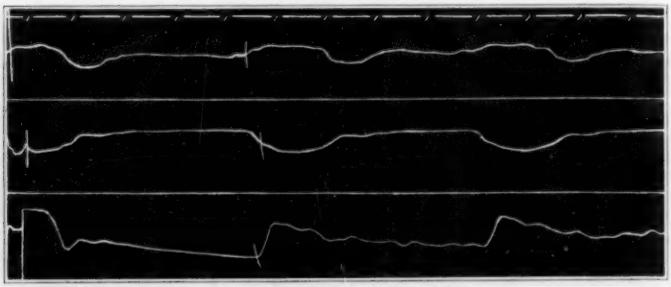

Fig. 3 (patient H. A.).—The graph demonstrates the oppositely directed movement of the right and left sides of the chest, respectively, (seesaw movement) in the presence of tricuspid regurgitation. The lower graph is for the radial artery; the middle graph, for the sixth intercostal space, 4 cm. outside the left midclavicular line, and the upper graph, for the midaxillary line on the right side over the seventh rib.

also another factor, i. e., the inadequate filling of the left side of the heart; for during systole the greater quantity of blood regurgitates from the right side of the heart into the veins and a comparatively scanty amount of blood flows through the lesser circulation. This is explained roentgenologically by the marked transparency of the pulmonary fields.

Tricuspid regurgitation, either endocarditic or muscular in origin, and adhesive pericardial disease have important signs in common—the diffuse systolic depression of the precordium, sometimes also a diastolic propulsion of the thoracic wall; occasionally one finds the reduplicated second sound described by Friedreich. Ignorance of these conditions frequently leads to diagnostic errors: tricuspid regurgitation is con-

fused with obliterative pericardial disease, and indications for surgical intervention are established. For instance, the Viennese surgeon Ewald reported the case of a woman aged 33 who showed signs of cardiac failure following articular rheumatism and a widespread systolic depression of the precordium. A well known clinician assumed this to be obliterative pericardial disease and sent her to the surgeon for cardiolysis. At operation, however, the pleura and pericardium were observed to be delicate and transparent. The patient died as a result of the operation, and necropsy revealed a lesion of the mitral valve, together with organic tricuspid regurgitation.

Systolic depression of the thoracic wall is especially frequent in cases of myopathy with muscular tricuspid insufficiency. Here the erroneous assumption of obliterative pericardial disease has even led to a new indication for Brauer's operation. It was found that resection of the ribs, made as the result of an erroneous interpretation of the indications, was followed by an improvement in the condition of the patient. Hence, Brauer's operation has been recommended by certain French authors (Lenormant and d'Aubigné [5] and Worms and d'Aubigné [6]) in cases of enlargement of the heart with systolic depression of the thoracic wall, though they did not recognize that the accompanying tricuspid regurgitation was the cause of the pulsation of the wall.

In order to avoid confusing tricuspid regurgitation with obliterative pericardial disease the hand should be placed over the hepatic area in every case in which systolic depression of the precordium is noted. The characteristic strong systolic propulsion of tricuspid regurgitation is easily recognized.

SUMMARY

As in cases of aortic regurgitation, one finds in many instances of tricuspid regurgitation a diffuse systolic depression of the precordium. This is caused by the complete emptying of the right ventricle.

The aspiratory effect on the thoracic wall due to the reduction of the ventricular volume during the systolic efflux is particularly pronounced in tricuspid regurgitation, since the dilated right ventricle empties during systole in two directions simultaneously. In addition, the most important factor for the neutralization of the systolic fall of the intrathoracic pressure, i. e., the influx of venous blood, is eliminated by regurgitation into the veins. Regurgitation into the liver leads to a forceful propulsion of the right upper and lower portions of the

5. Lenormant, C., and d'Aubigné, R. M.: La thoracectomie précordiale dans les symphyses et certaines hypertrophies cardiaques, J. de chir. **31**:161, 1928.

6. Worms, R., and d'Aubigné, R. M.: Une observation de thoracectomie précordiale pour symphyse du péricarde, Bull. Soc. de pédiat. de Paris **26**:219, 1928.

chest and occasionally also to a jerky shift of the whole chest from left to right; the latter finding is particularly characteristic of this type of valvular lesion. The propulsion of the right side of the chest in association with the systolic depression over the cardiac area results in a seesaw movement, which Volhard was the first to describe for tricuspid regurgitation. No significance should be attributed to the systolic filling of the right auricle in the etiology of this pulsatory phenomena.

In contrast to aortic regurgitation, the apical thrust is absent as a rule in cases of tricuspid regurgitation. This is due to the fact that the left ventricle is poorly filled and is pushed away from the anterior wall of the chest by the much enlarged right ventricle. There is forceful filling of the right ventricle because of the high venous pressure, and occasionally one finds an abrupt diastolic pulsation of the thoracic wall, very similar to the diastolic cardiac thrust in the presence of adhesive pericardial disease. Likewise, Friedreich's reduplicated sound is occasionally heard. Confusion of tricuspid regurgitation with adhesive pericardial disease is therefore not uncommon, and only a careful observation of the forceful hepatic regurgitation pulse will insure against diagnostic error.

The systolic depression is often inhibited in the presence of a combination of tricuspid regurgitation with mitral stenosis, because of the opposing force of the change in shape of the heart.

EFFECTS OF A VITAMIN B_1 CONCENTRATE

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EFFECT ON PERISTALSIS

Controversial opinions have been expressed as to whether vitamin B_1 deficiency occurs to any appreciable extent in otherwise healthy persons under the conditions of dietary habits prevailing in the United States.[1] It is evident that a more or less pronounced deficiency may develop as a result of drastic voluntary dietary restrictions or in pathologic conditions associated with inanition, impaired utilization of food or consumption of food poor in vitamin B_1, e. g., gastric ulcer, chronic ulcerative colitis, colectomy or pernicious vomiting of pregnancy. Recognition of the deficiency is difficult, owing to the paucity of clinical symptoms. Beriberi is known to have developed in a patient with a short-circuited small intestine [2] and in patients with other lesions responsible for gastro-intestinal disorders.[3] A lack of vitamin B_1 causes an impairment of digestive secretions and of oxidation of carbohydrates; it also lowers the tone of the gastro-intestinal musculature and causes anorexia. Hence, a deficiency of vitamin B_1 may aggravate the intes-

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The vitamin B_1 concentrate employed was supplied by Eli Lilly & Co. One cubic centimeter represents 150 Sherman-Chase units of vitamin B_1. The concentrate has not been offered for sale and was supplied exclusively for experimental purposes.

1. Cowgill, G. R.: Vitamin B_1 in Relation to the Clinic, J. A. M. A. **98**:2282 (June 25) 1932. Alvarez, W. C.: Opinions of Four Hundred and Seventy Physicians in Regard to Advantages and Disadvantages of Using Bran and Roughage, Minnesota Med. **14**:296, 1931. Harris, L. J.: The Significance of Vitamins in Practical Experience, Brit. M. J. **2**:367 (Aug. 26) 1933. Clausen, S. W.: The Influence of Nutrition upon Resistance to Infections, Physiol. Rev. **14**:309, 1934.

2. Urmy, T. V.; Ragle, B. H.; Allen, A. W., and Jones, C. M.: Beriberi Secondary to Short-Circuited Small Intestine, New England J. Med. **210**:251 (Feb. 1) 1934.

3. Goudsmit, J.: Deficiency Symptoms in Chronic Gastro-Intestinal Diseases, Nederl. tijdschr. v. geneesk. **78**:3123 (July 7) 1934. Riesman, D., and Davidson, H. S.: Beriberi Following Drastic Voluntary Dietary Restriction, J. A. M. A. **102**:2000 (June 16) 1934. Larimore, J. W.: Chronic Ulcerative Colitis, ibid. **90**:841 (March 17) 1928.

tinal atony accompanying threatened or incipient paralytic ileus, a frequent aftermath of major operation, particularly laparotomy. Consequently, the deduction is justified that administration of vitamin B_1 in certain surgical conditions may be of therapeutic value, especially because a deficiency may lower the patient's resistance to infection. The desirability of administering vitamin B_1 in these conditions is enhanced by the observation that vitamin B_1 is not stored in the body and therefore a continuous optimal intake is necessary.

The difficulty of obtaining an absolutely pure product was not considered as a discouraging factor, because valuable information concerning the physiologic importance of many substances has been gathered before the completion of knowledge concerning their chemical identities.

METHOD

In the first series of experiments ileostomy was performed on eight dogs of both sexes, and peristalsis was recorded by the balloon-tambour method, a finger-cot being used as a balloon. Ileostomy was chosen in preference to a Thiry-Vella fistula, as it was considered a more physiologic method. The balloon was inflated with air, and a hydrostatic pressure of from 12 to 15 cm. was maintained in it. The balloon was inserted in the cephalad direction, precautions being taken not to have it expelled by the propulsive motions of the gut. Introduction of the balloon into the efferent loop may lead to failure to register intestinal movements, owing to a disproportion between the diameter of the balloon and the size of the cecum into which it may inadvertently be pushed. The peristalsis was recorded ordinarily for twenty minutes before and for from forty-five to sixty minutes after the injection of varying amounts of the concentrate. Concomitant respiratory tracings were made.

In the majority of the experiments a pronounced effect of the vitamin B_1 concentrate was noticed. The minimum effective dose was calculated to be approximately 0.7 cc. of the concentrate per kilogram of body weight if injected intravenously. In some instances the increase in tone was especially marked; in others the frequency and the amplitude of movements increased, while occasionally rhythmic contractions appeared. A combination of these results also was sometimes observed. The most conspicuous effect lasted on an average from three to ten minutes. Repeated injections on successive days were usually followed by identical reactions. Individual differences in the response of peristalsis to vitamin B_1 in various animals were noticed. Hypodermic injections were followed by less pronounced stimulation.

For the sake of comparison, the effects of several other substances on intestinal peristalsis were studied in the same animals. Ergotamine tartrate, pitressin and small doses of the dimethylcarbamic ester of m-oxyphenyltrimethylammonium-methylsulfate (prostigmin) had no noticeable effect, while physostigmine and acetylbetamethylcholine (mecholyl) produced, with the dose employed, increase of tonus, frequency and amplitude of contractions comparable to, but less pronounced than, those caused by the vitamin B_1 concentrate.

A crystalline product of vitamin B_1[4] was tested on two dogs. The results obtained were identical with those obtained with the vitamin B_1 concentrate. A

4. This crystalline product of vitamin B_1 was supplied by Merck & Co., Inc.

subcutaneous injection of 10 mg. of atropine did not inhibit the stimulating effect of an intravenous injection of 7 cc. of vitamin B_1 concentrate given ten minutes later.

In another series of experiments varying doses of the vitamin B_1 concentrate were added to Ringer's solution in which a segment of small intestine of a guinea-pig was immersed. The resulting spastic contraction was sometimes followed by an increase in the frequency and amplitude of the peristaltic movement. In several instances peristalsis became erratic.

EFFECT ON BLOOD PRESSURE

Muscular weakness and lassitude of dogs after intravenous injections of large doses of vitamin B_1 suggested a systemic effect. Therefore, a study of the effect of vitamin B_1 on the blood pressure was undertaken. The pressure was recorded by means of a cannula introduced into the carotid artery. A pronounced and abrupt fall in blood pressure was observed in every instance in dogs and rabbits. The effect of the crystalline product also was tested. In one experiment no effect was noticed, while in another a slight fall in blood pressure was recorded. A rapid return to the normal height was usually observed a few minutes after the injection of the vitamin B_1 concentrate. An injection of 0.25 cc. of a 1:1,000 solution of epinephrine preceding an intravenous injection of 2 cc. of the vitamin B_1 concentrate did not prevent a sharp drop in blood pressure. The fall in blood pressure was slight after the subcutaneous injection of the vitamin B_1 concentrate.

Attempts were made to identify the substance responsible for the depressor effect of the vitamin B_1 concentrate on the blood pressure. Barsoum and Gaddum [5] made the observation that the presence of histamine in the bath renders a strip of rectal cecum of a fowl insensitive to doses of histamine sixty times as large as those which had previously caused contraction. These facts can be made the basis of a method of identification of active substances in tissue extracts. Similar experiments were performed with a strip of the small intestine of a guinea-pig and on the proximal portion of the rectal cecum of a chicken. When 0.00000004 cc. of the vitamin B_1 concentrate in 1 cc. of Ringer's solution was given a steep rise in the tonus and an increase in the amplitude of the contractions were produced. After this effect had subsided, the same dose of histamine had no effect, pointing to the presence of histamine in the vitamin B_1 concentrate.

Major [6] has stated that histamine produces a rise in the blood pressure of atropinized rabbits, while choline has no effect. According

5. Barsoum, G. S., and Gaddum, J. H.: The Pharmacological Estimation of Adenosine and Histamine in Blood, J. Physiol. **85**:1 (Aug. 22) 1935.

6. Major, R. H., and Weber, C. J.: Observations on the Depressor Substances in Certain Tissue Extracts, J. Pharmacol. & Exper. Therap. **37**:367 (Nov.) 1929.

to Vincent,[7] choline causes a fall in blood pressure in etherized rabbits, while histamine has no effect or produces a rise; in atropinized rabbits, according to this author, choline causes a marked rise in blood pressure, while histamine has no effect or is followed by a rise in pressure. The rise in pressure in etherized rabbits after the intravenous injection of the vitamin B_1 concentrate and the absence of an effect in an atropinized rabbit apparently demonstrated the presence of choline in the concentrate, while no conclusion could be reached as to the presence of histamine.

These depressor substances may be undesirable under many circumstances. Therefore, the company which supplied the product made further attempts to purify it. The intravenous injection of a 2 cc. of a new lot of vitamin B_1 concentrate produced a slight drop in blood pressure in a dog. An attempt was made to reproduce the same degree of fall in blood pressure with histamine. For this purpose, 0.0005 mg. was required. In other words, the effect of 1 cc. of the new concentrate corresponded to the effect of 0.00025 mg. of histamine. In an etherized rabbit 0.2 mg. of histamine produced a slight rise in the blood pressure. After the subcutaneous injection of 2 mg. of atropine the same dose of histamine caused a slight rise, followed by a marked fall in pressure and death of the animal. After this preliminary experiment 2 cc. of the new concentrate was injected intravenously into an etherized rabbit. A slight fall in blood pressure followed. Fifteen minutes after the subcutaneous administration of the same amount of atropine, 2 cc. of the vitamin B_1 concentrate had no effect on the blood pressure. One milligram of histamine produced a sharp drop in pressure. The results of these experiments point to the presence of choline and the absence of an amount of histamine capable of producing a rise in pressure.

The effect of the new concentrate on intestinal contractions was studied on a strip of small intestine from a guinea-pig. It was found that 0.025 cc. of the concentrate per cubic centimeter of Ringer's solution had no effect, while 0.0005 mg. of histamine produced a spastic contraction. In other words, 1 cc. of the new concentrate contained less than 0.2 mg of histamine. In another series of experiments a strip of rabbit intestine was used. Gradually increasing doses of the new lot were employed, starting with 0.00000001 cc. It was found that 0.04 cc. of concentrate per cubic centimeter of Ringer's solution caused a lowering of the amplitude of the intestinal contractions; 0.00002 mg. of histamine had no effect, while 0.01 mg. was responsible for a rise in the amplitude of the contractions. The contractions became

7. Vincent, S., and Curtis, F. R.: Nature of Depressor Substance or Substances in Tissue Extracts, Lancet **1**:1142 (June 12) 1926.

still larger after the addition of 0.1 mg. of histamine. In other words, in these experiments no detectable amount of histamine could be found in the new concentrate.

COMMENT

The old vitamin B_1 concentrate exerted a stimulating effect on the tonus of the small intestines of dogs and on the frequency and amplitude of peristaltic movements. It also produced a sharp drop in blood pressure in dogs and rabbits. In one experiment a slight fall in blood pressure was observed after the injection of a crystalline product. This observation suggests that the effect was possibly not due wholly to impurities. The concentrate apparently contained histamine and choline. The presence of these depressor substances is not necessarily an undesirable feature, because the field of usefulness of histamine and related substances is gradually becoming wider. For instance, they are recommended in the treatment of rheumatic conditions, peptic ulcers and certain vascular lesions. However, it seems that they should be avoided in many conditions, particularly those associated with low blood pressure. Hence, the attempt was made to eliminate the depressor substances from the concentrate. The new batch apparently contained extremely small doses of histamine and probably also choline, but there was no stimulating effect on intestinal contractions. The comparison of the effect of the old and that of the new batch suggests that in the process of purification the elimination of depressor substances deprived the concentrate of the effect of peristalsis. A conclusion is allowed that the stimulating effect of the old batch on intestinal contractions was due to the presence of histamine and possibly also of choline. If this assumption holds true, it remains a matter of conjecture whether or not the intestinal atony characteristic of vitamin B_1 deficiency is a direct result of a lack of vitamin B_1 and not of histamine and choline. Further investigations must show whether B_1 avitaminosis is accompanied with a diminution in the amount of histamine and choline in the body. The genesis and mechanism of a lack of these substances remain obscure.

The knowledge of the presence of depressor factors in vitamin B_1 concentrates is of great importance, as it helps to outline the indications and contraindications for the use of these products. It also points the direction in which the further process of purification of vitamin B_1 concentrate must go. Cowgill [8] has justly stated that recent perfection of methods for preparing vitamin B_1 concentrate suitable for injections should lead to more extensive trial of this type of therapy.

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8. Cowgill, G. R.: The Vitamin B Requirement of Man, New Haven, Yale University Press, 1934, p. 20.

TRACTION DIVERTICULUM OF THE ESOPHAGUS

ROENTGENOGRAPHIC DEMONSTRATION; SYMPTOMS NOTED IN A SERIES OF TWENTY-SIX PATIENTS

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Traction diverticulum of the esophagus, noted with relative frequency in adults at necropsy [1] and demonstrable to some degree roentgenographically [2] has been generally thought to be without symptoms and of minor clinical importance.[3] Among ten patients reported on in 1932 [2] and among sixteen additional patients in whom the condition was discovered under the conditions and method outlined in that report, symptoms recurred with such frequency as to cast doubt on the theory of absence of symptoms with this lesion.

This paper will present an analysis of the symptomatology and certain findings in twenty-six cases of traction diverticulum situated in the midthird of the thoracic portion of the esophagus, in close proximity to the bifurcation of the trachea and to the hilus of the left lung.

ANALYSIS OF COMPLAINTS

Symptoms were attributed to the diverticulum by ten (38.5 per cent) of the twenty-six patients. In eight cases these symptoms were the patient's chief complaint, while in the remaining two cases (that of a

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1. Starck, H.: Die Divertikel der Speiseröhre, Leipzig, F. C. W. Vogel, 1900. Heinen, W.: Ein Beitrag zur Kenntnis der an der Bifurkation der Trachea gelegenen Divertikel des Oesophagus, Frankfurt. Ztschr. f. Path. **1**:176-186, 1907. Kragh, J.: Diverticules tuberculeux, dits diverticules de traction, l'oesophage d'un boeuf, Compt. rend. Soc. de biol. **85**:755-757, 1921.

2. Sturtevant, M.; Shapiro, L. L., and Wallace, R. P.: Traction Diverticulum of the Esophagus, Am. J. Roentgenol. **27**:187-192 (Feb.) 1932.

3. Barrett, N. R.: Diverticula of the Thoracic Esophagus, Lancet **1**:1009-1011 (May 13) 1933. Heacock, C. H.: Diverticula of the Thoracic Portion of the Esophagus, South. M. J. **23**:517-520 (June) 1930. Hill, W.: Pharyngeal and Esophageal Diverticula, Brit. M. J. **2**:1163-1169 (Dec. 18) 1926. Lahey, F. H.: Surgical Management of Pharyngo-Oesophageal Diverticulum, Surg., Gynec. & Obst. **51**:227-236 (Aug.) 1930. Carmen, R. D.: The Roentgen Diagnosis of Diseases of the Alimentary Canal, ed. 2, Philadelphia, W. B. Saunders Company, 1921. Vinson, P. P.: Diverticula of the Thoracic Portion of the Esophagus, Arch. Otolaryng. **19**:508-513 (April) 1934.

man with cardiac disease and that of a destitute, undernourished woman during the menopause) esophageal symptoms were of secondary importance. Three of the ten patients had had continuous symptoms, in three the symptoms showed periodicity, while the remaining four were seen soon after the onset of their symptoms.

Pain behind the sternum was felt by six patients. A sensation of weight or heaviness was complained of by four and burning by three, while sudden, sharp, short, sticking, dull, constant, choking and constricting were the terms used once each to describe the discomfort. Occasionally food would increase the pain, but this was neither a frequent nor a constant finding. The intensity of the pain varied from mild to severe and bore no relationship to position of the body, respiration or time of day. Usually the pain was referred to the midsternum, but when severe it was not localized and was described as in the chest. Four patients experienced radiation of the pain; by two it was referred laterally to the ribs below the axilla and by two to the interscapular region.

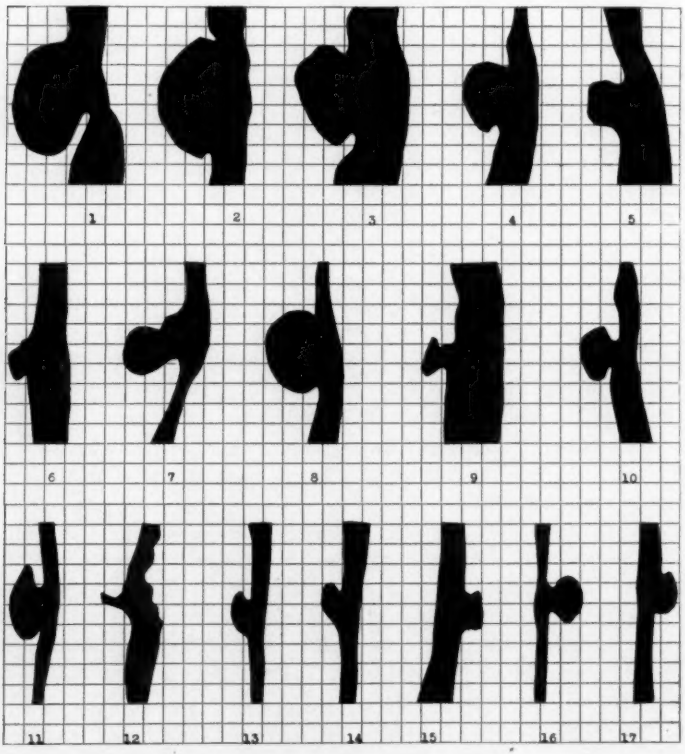
Dysphagia, distinct from substernal pain, was experienced by six patients. Swallowing was not only difficult but painful. Descriptive terms used were discomfort, pain, sticking, heaviness and soreness. The degree of dysphagia varied from mild to severe, with necessary restriction of the diet to liquids and soft foods.

Hematemesis occurred in three cases, and in two it was the only complaint. In two the loss of blood was moderate and was described as small and as a cupful, respectively. In these two cases regurgitation was spontaneous and unassociated with nausea or retching. The third patient on two occasions had a copious hemorrhage, which was estimated at more than a pint (500 cc.), of bright red blood, containing some coffee-ground material. Immediately after the hemorrhage he felt weak and faint. The erythrocyte count fell to 3,500,000, with a hemoglobin (Sahli) content of 45 per cent. In 2 cases there was melena after the hemorrhage.

Other symptoms of minor importance and infrequent occurrence were eructations, simple vomiting, hiccup, pain high in the epigastrium and weakness.

An attempt was made to ascertain whether other findings of this series were in any way related to the causation of symptoms. The average age of the patients who showed symptoms was 53.7 years; the symptomless patients were on an average of 4 years older than those with symptoms. There were two and one-half times more men than women in each group, and this approximated the sex relationship of all patients examined. A single diverticulum was present in each case in which there were no symptoms and, except in two cases in which there

were multiple pouches, in all the cases in which there were symptoms. In the cases of symptomless diverticulum the long axis of the sac was directed to the left obliquely (anteriorly and to the left) in thirteen and to the right obliquely in three. In four of the cases in which there were symptoms the direction was to the left obliquely and in six cases to the right obliquely. This predominance of direction of the sac to the



Exact tracings of the diverticula on centimeter graph paper from the roentgenograms made with a tube-film distance of 30 inches (75 cm.). Symptomless diverticula: *1, 2, 5, 6, 8, 9, 10, 13, 14* and *17;* mild symptoms, *4, 7, 11* and *16;* severe symptoms, *3, 12* and *15.*

right obliquely in those patients with symptoms is unexplained. No definite relationship between the size of the sac and the occurrence of symptoms could be established. Several of the smallest sacs were noted in patients with the most severe symptoms, and a number of the largest sacs produced no symptoms whatever (figure).

SUMMARY

Substernal distress, dysphagia or hemorrhage, either alone or in combination, occurred in the ten cases of traction diverticulum associated with symptoms. In a few the symptoms were chronically present, but in the majority a period of comfort separated the attacks.

CONCLUSION

Evidence is presented to show that traction diverticulum of the esophagus caused symptoms in slightly more than a third of a small series in which diagnosis was established during life roentgenographically.

LEUKEMIA WITHOUT LEUKOCYTOSIS (ALEUKEMIC MYELOSIS) AND WITHOUT SPLENOMEGALY

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It is well known that leukemia may occur without leukocytosis. In such cases the clinical picture of weakness and pallor and the varying degrees of lymphadenopathy, splenomegaly and hepatomegaly, with the blood picture of anemia and thrombopenia and the presence of myeloblasts in the stained blood film, make the diagnosis possible. The anatomic findings in the cases hitherto reported [1] show a similarity to the anatomic picture in true leukemia. There is, however, relatively little to be found in the medical literature on the occurrence of leukemia without splenomegaly. In a recent review [2] on leukemia it was mentioned that there are instances in which no splenic enlargement is noted. Hirschfeld [3] reported four cases of leukemia without splenomegaly, Ordway and Gorham [4] reported one case and Kracke and Garver [5] also described one case. Recently Parkes Weber [6] reported a case of aleukemic myelosis without splenic enlargement in which the condition

Supported by a grant from the Christine Breon Fund for Medical Research.

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1. Pinkerton, H.: Aleukemic Leukemia and Atypical Leukemoid Conditions: Report of Seven Cases Including One of Acute Erythroblastosis, Arch. Path. **7**: 567 (April) 1929. Baldridge, C. W., and Fowler, W. M.: Aleukemic Myelosis, Arch. Int. Med. **52**:852 (Dec.) 1933.

2. Rosenthal, Nathan, and Harris, W.: Leukemia: Its Diagnosis and Treatment, J. A. M. A. **104**:702 (March 2) 1935.

3. Hirschfeld, H.: Die generalisierte aleukämische Myelose und ihre Stellung im System der leukämischen Erkrankungen, Ztschr. f. klin. Med. **80**:126, 1914.

4. Ordway, T., and Gorham, W.: The Diagnosis and Treatment of Diseases of the Blood, in Christian, H. A.: Oxford Monographs on Diagnosis and Treatment, London, Oxford University Press, 1930, vol. 9.

5. Kracke, R. R., and Garver, H. E.: Hypocytic Leukemia (Aleukemic Leukemia), Internat. Clin. **4**:37, 1935.

6. Weber, F. P.: Aleukemic Myelosis of the Leucopenic Type, Clinically Simulating Chronic Aplastic Anaemia, Quart. J. Med. **1**:409, 1932.

clinically simulated aplastic anemia. He stated that many cases in which the clinical diagnosis was aplastic anemia have doubtless been examples of aleukemic myelosis.

During the past several years in the wards of the University of California Hospital there have been an unusual number of patients with leukopenia [7] with an abnormal leukocyte picture, showing varied types of involvement and presenting difficult diagnostic problems. Among these was a group of patients with leukemia not associated with splenomegaly. Myeloid hyperplasia of the bone marrow consistent with leukemia was noted in all these cases. It is our purpose in this paper to present the histories of five of these patients, to classify the condition as leukemia without splenomegaly and without leukocytosis and to discuss the clinical recognition of this condition.

REPORT OF CASES

CASE 1.—E. P., a white woman aged 21, was admitted to the University of California Hospital on Feb. 2, 1932, complaining of weakness, dyspnea, menorrhagia and bleeding gums. Nine months prior to the patient's entry into the hospital her illness began with an attack of nausea, vomiting, diarrhea and headache, accompanied with a temperature ranging between 99 and 100 F. After an examination her physicians told her that her hemoglobin value was 27 per cent, that she had leukopenia and that immature white blood cells were present in the stained film. She was given three transfusions, after which the symptoms subsided, and she was told that the hemoglobin value had increased. Two months later the symptoms recurred, and the hemoglobin value was reported to be 44 per cent. During the next six months the patient received transfusions at intervals of from two to three weeks. Within the week prior to entry into the hospital she was given three transfusions each of 500 cc. of whole blood.

Physical Examination.—The patient appeared well developed and well nourished. There was no evidence of infection in the skin, ears, nose or throat. The gums appeared swollen and spongy, and there was slight bleeding around the gingival margins; but signs of suppuration or active inflammation were not present. There were a few scattered fading areas of ecchymosis on the skin. Lymph nodes, averaging in size from 1 to 2 cm., were present in the anterior cervical triangles, and a few nodes were felt in the axillae, but none could be palpated in the epitrochlear or inguinal regions. The heart was not found to be enlarged on percussion, and no cardiac murmurs were audible on deep inspiration. The edge of the liver descended 2 cm. below the right costal margin, but the spleen could not be palpated.

Laboratory Data.—The blood count showed: erythrocytes, 4,310,000 per cubic millimeter; hemoglobin, 94 per cent (12.9 Gm.) Sahli, and leukocytes, 7,600 per cubic millimeter. The differential count showed: segmented polymorphonuclear leukocytes, 39 per cent; nonsegmented leukocytes, 2 per cent; lymphocytes, 45 per cent; monocytes, 3 per cent; myelocytes, 4 per cent; myeloblasts, 5 per cent, and unclassified immature forms, 2 per cent. One nucleated red blood

7. Mettier, S. R., and Olsan, H. T.: The Clinical Significance of Leucopenia with Special Reference to Idiopathic Neutropenia, Ann. Int. Med. **6**:855, 1933.

cell was seen per hundred white blood cells. The number of platelets was greatly diminished. Cultures made of material from the stools failed to show any growth of pathogenic organisms.

Course of the Illness.—Three days after the patient's admission to the hospital the leukocyte count was 4,600 per cubic millimeter. Examination of a stained film showed that 4 per cent of the cells were large and round, with basophilic cytoplasm and a nucleus which contained from 4 to 6 nucleoli. These cells were considered myeloblasts. On the same day a slight decrease in the erythrocyte count and hemoglobin content was noted. From this time on there was a progressive drop in the level of the erythrocytes and leukocytes. On February 25 the blood count showed: hemoglobin, 50 per cent; erythrocytes, 1,780,000 per cubic millimeter, and white blood cells, 1,700 per cubic millimeter. The differential count showed: segmented polymorphonuclear leukocytes, 44 per cent; nonsegmented leukocytes, 20 per cent; eosinophils, 2 per cent; lymphocytes, 16 per cent; monocytes, 2 per cent; myelocytes, 10 per cent, and myeloblasts, 6 per cent. One nucleated red blood cell was seen per hundred white blood cells. There was marked achromia of the red blood cells. A sparse number of platelets was noted.

At this time continuous oozing of blood from the gums and profuse menses had been present for a week. Administration of iron and ammonium citrates, 6 Gm. daily, solution of potassium arsenite U.S.P. and roentgen irradiation over the long bones failed to alleviate the patient's symptoms. On February 26 and 29 the patient received transfusions, each of 500 cc. of whole blood, which were followed by a slight increase in the number of erythrocytes and in the hemoglobin content with a slight lessening of bleeding. There was persistent leukopenia, with approximately 1,500 white blood cells per cubic millimeter. Three days prior to the patient's death the white blood cell count was 1,350 per cubic millimeter. The differential count was: segmented polymorphonuclear leukocytes, 18 per cent; nonsegmented leukocytes, 23 per cent; eosinophils, 4 per cent; lymphocytes, 25 per cent; monocytes, 4 per cent; myelocytes, 18 per cent; myeloblasts, 6 per cent, and unclassified immature forms, 2 per cent. There were 2 nucleated red blood cells per hundred white blood cells. Anisocytosis and poikilocytosis were marked, and the number of platelets was greatly decreased.

About five days after the last transfusion there was evidence of hemorrhage from the bladder and gastro-intestinal tract. The patient died on March 6. During the five weeks she was under observation in the hospital the temperature varied from 36.8 C. (98.2 F.) in the mornings to as high as 37.4 C. (99.3 F.) in the afternoons.

Clinical Diagnosis.—The clinical diagnosis was aleukemic myelosis with slight leukemic metaplasia of the cervical lymph nodes.

Biopsy of a Cervical Lymph Node.—On February 6 a specimen from a cervical lymph node was removed for biopsy. The sections showed that the architecture of the lymph node had been largely replaced by tumor cells which varied somewhat in shape, size and character. Many of these cells appeared to be overgrown germinal centers and reticulum cells, but still more appeared to be of myeloid types. The latter cells had rather abundant and large indented nuclei, many of which showed mitosis. In addition there were many nucleated red blood cells, and the nuclei of these cells were seen in all stages of degeneration and fragmentation. In the vicinity of the myelocytic cells were many young polymorphonuclear leukocytes. Among the myelocytic cells there were neutrophilic and eosinophilic types. The cellular structure of the node was believed to be

consistent with the myeloid and erythroblastic metaplasia occurring in a myelogenous type of leukemia. The diagnosis was leukemic involvement of the lymph node.

Gross Postmortem Examination.—The body appeared to be well developed and fairly well nourished. There was marked pallor of the skin and mucous membranes. In the skin over the forehead, cheeks, chest, abdomen, arms and legs there were numerous areas of petechial hemorrhage, measuring up to 3 mm. in diameter. The gums were greatly swollen, spongy and bluish, and from them exuded a sanguineous fluid. Lymph nodes, averaging 1 cm. in diameter, were present in the anterior cervical triangles, the axillae and the inguinal regions. The postmortem examination was limited. Through a suprapubic incision the abdominal viscera were examined. A specimen of bone marrow was obtained from the right femur.

Internal Organs: There was no evidence of septic peritonitis. Many petechial hemorrhages were seen in the peritoneum. The edge of the liver projected 1 cm. below the right costal margin.

Spleen: The spleen weighed 190 Gm. The surface appeared smooth and glistening. Cut section showed that the pulp was slightly softer in consistency than normal but could not be readily scraped away on the edge of a knife. The size of the malpighian bodies appeared normal.

Pelvic Organs: The pelvic organs were removed in toto. The bladder when opened contained a large blood clot, and the mucosa was covered with sanguineous material. The uterine cavity was filled with hemorrhagic fluid. There was no evidence of suppuration. The ovaries appeared to be of normal size; in one there was a cyst which contained recently clotted blood.

Lymph Nodes: The mesenteric and retroperitoneal nodes were slightly enlarged. The largest one seen measured 0.5 cm. in length. On cut section the tissue appeared firm and reddish pink.

Bone Marrow: A specimen of bone marrow was removed from the upper third of the left femur. It appeared reddish gray and was of firm consistency.

Microscopic Postmortem Examination.—The bone marrow was markedly cellular and made up of blood-formative cells and a slight amount of undifferentiated connective tissue. There were large numbers of myelocytes and myeloblasts forming a compact hyperplastic leukopoietic tissue. Only occasional small foci of erythropoiesis were noted.

Spleen: The spleen showed a nearly normal preservation of architecture. The centers of the malpighian bodies were composed of large cells with pale eosinophilic cytoplasm and vesicular nuclei. In the sinusoidal spaces were small numbers of myeloid elements similar to those observed in the bone marrow. There were a few cells that resembled nucleated red blood cells.

Liver: About the portal spaces in the parenchyma were small accumulations of abnormal cells. The cells were chiefly of a large mononuclear type, and an occasional cell contained a mitotic figure.

Lymph Node: A section of a retroperitoneal lymph node showed slight alteration from its normal architecture. The follicles were smaller than normal. Scattered throughout the tissues between the lymphoid cells were young myeloid cells.

Postmortem Diagnosis.—The diagnosis was aleukemic myelogenous leukemia, with leukemic bone marrow; moderate leukemic infiltration of the liver; slight myeloid metaplasia of the spleen and lymph nodes, and purpuric manifestations in the skin, bladder, uterus and gastro-intestinal tract.

Comment.—The onset of this patient's illness was characterized by symptoms arising from the gastro-intestinal tract and associated with fever and leukopenia. After the patient was admitted to the hospital it was thought that the leukopenia might have been due to an abnormal response of the bone marrow to sepsis in the intestinal tract. Cultures of material obtained from the stools and blood failed to show pathogenic organisms. The diagnosis of aleukemic myelosis was suggested by the appearance of myeloblasts in the stained blood film and was substantiated by the myeloid metaplasia of the cervical lymph node removed for biopsy. Throughout the course of the illness the spleen was not enlarged. Pathologic observations essential for the diagnosis of aleukemic myelosis were made post mortem.

CASE 2.—T. B., a white American man aged 38, entered the University of California Hospital on July 20, 1933. Eight months prior to entry he had an attack of fever and weakness, associated with muscle pain. His physician made the diagnosis of influenza. The patient was in bed one week; afterward he regained his strength slowly. During the winter he did not feel as well as formerly and continued to complain of weakness, aching of muscles and nausea but no vomiting. About one month before entry roentgenograms were taken of the gastro-intestinal tract, and a diagnosis of peptic ulcer was made. For the patient were prescribed rest in bed and a modified Sippy regimen, with milk feedings and alkaline powders. However, he continued to be weak. There was no history of blood in the stools or of diarrhea. Ten years previously the patient had pleurisy with effusion; after thoracentesis he recovered completely. There was no history of other infections.

Physical Examination.—The patient appeared well developed and well nourished. There was marked pallor of the skin. The heart was not enlarged on percussion; its action was regular, but a soft, blowing systolic murmur was heard over the mitral and pulmonic regions. Neither the liver nor the spleen could be felt. There was no enlargement of the superficial lymph nodes. Slight pyorrhea alveolaris was noted, but there was no evidence of respiratory or genito-urinary infection.

Laboratory Data.—The blood count on July 20 showed: hemoglobin, 55 per cent (7.7 Gm.) Sahli; erythrocytes, 3,270,000, and leukocytes, 2,300. The differential count showed: polymorphonuclear leukocytes, 7 per cent; nonsegmented leukocytes, 22 per cent; lymphocytes, 42 per cent; monocytes, 26 per cent, myelocytes, 1 per cent, and unclassified cells, 2 per cent. Two nucleated red blood cells were seen per hundred leukocytes in the stained film. The icterus index was 7.5. There were 3.4 per cent reticulocytes. The platelets were greatly reduced in number.

Course of the Illness.—The patient remained under observation in the hospital for three weeks, during which time the anemia and the leukopenia persisted with only slight variation. There was no apparent hematopoietic reaction to liver extract given either parenterally or by mouth. The patient was discharged on August 10.

Because of failure to gain in strength, the patient returned to the hospital on August 28. On this occasion neither lymphadenopathy nor enlargement of the spleen was apparent. The blood count showed: hemoglobin, 43 per cent (6.1 Gm.) Sahli; erythrocytes, 2,460,000 per cubic millimeter; leukocytes 2,450 per cubic millimeter and reticulocytes, 1.6 per cent. The differential count showed: seg-

mented polymorphonuclear leukocytes, 2 per cent; nonsegmented leukocytes, 14 per cent; eosinophils, 1 per cent; lymphocytes, 28 per cent; monocytes, 14 per cent; myelocytes, 10 per cent, and promyelocytes and myeloblasts, 31 per cent. There was a slow and gradual decrease in the erythrocyte and leukocyte levels in spite of the use of the following therapeutic measures: liver extract, pentnucleotide, roentgen irradiation over the long bones and transfusions of whole blood. The patient's temperature showed a daily fluctuation from 36.8 to 38.6 C. (98.2 to 101.5 F.). On October 24 hemorrhages appeared in the retinas. The blood count showed: hemoglobin, 10 per cent (1.4 Gm.) Sahli; erythrocytes, 500,000 per cubic millimeter, and leukocytes, 980 per cubic millimeter. The differential count showed: segmented polymorphonuclear leukocytes, 8 per cent;

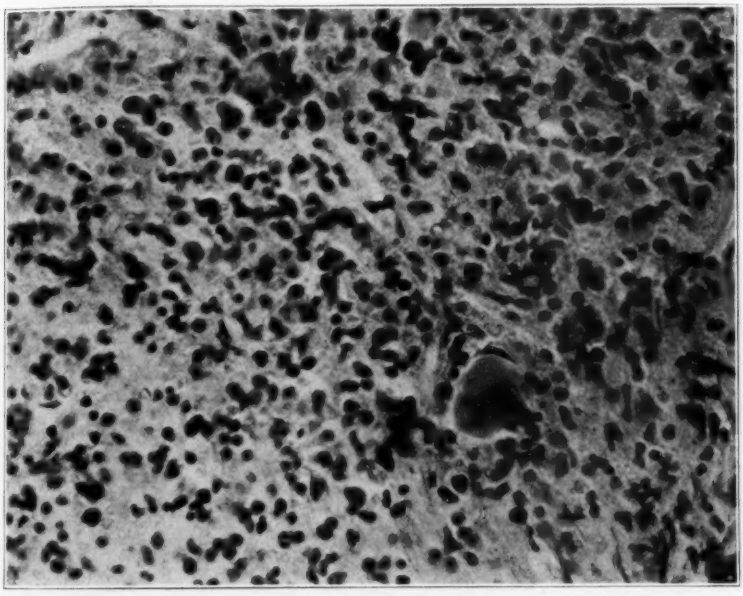

Fig. 1 (case 2).—Photomicrograph of the marrow removed from the sternum for biopsy; × 300. Note the increased cellularity.

nonsegmented leukocytes, 28 per cent; lymphocytes, 16 per cent; monocytes, 12 per cent; myelocytes, 20 per cent, and myeloblasts, 16 per cent. There were 40,000 platelets per cubic millimeter. At this time the tip of the spleen was barely palpable. Death occurred on October 27.

Clinical Diagnosis.—The diagnosis was aleukemic myelosis, with anemia and thrombopenia.

Biopsy of Sternal Marrow.—Sections of sternal marrow removed for biopsy showed hyperplasia but no fat. Groups of megakaryocytes were evident. The predominant type of cell had a large vesicular nucleus containing several chromatin masses and often darkly stained nucleoli. The outline of the cell was not distinct; the cytoplasm stained lightly and was light blue. Many of the cells

were in groups and appeared to be situated close to the endothelial cells of small capillaries. In an occasional cell relatively normal mitosis was present. A few eosinophilic myelocytes were to be seen. Small groups of erythroblasts and normoblasts could be distinguished, but they were not as predominant as the cells of the myeloid series. The diagnosis was hyperplasia of the bone marrow with increased myelopoiesis and erythropoiesis.

Gross Postmortem Examination.—The autopsy was performed by Dr. G. Biskind. The body was that of a well developed, slightly undernourished man. There was no evidence of purpura in the skin. Dentition was normal, and the gums were not abnormal. No masses were palpable in the abdomen. No lymph nodes could be palpated in the neck, axillae or inguinal region.

Internal Organs: There was no evidence of infection in the peritoneal cavity. The mesenteric lymph nodes were not enlarged, but there were a few large nodes around the head of the pancreas. The left pleural cavity was obliterated by old fibrous adhesions. There were no enlarged nodes in the mediastinum.

Heart: The heart weighed 380 Gm. The endocardium showed tigroid mottling, but there was no evidence of an inflammatory process.

Lungs: There was no evidence of any disease process.

Liver: The liver was enlarged and weighed 2,270 Gm. On the surface, which was brown, there were small, discrete, scattered zones of gray cellularity. These were not numerous. On cut section a certain amount of terminal congestion was evidenced by the prominence of the hepatic veins and lobules. The parenchyma was brown and soft, owing to an increase in the amount of fat. Gray cellular zones were relatively infrequent and small. The gallbladder was small, and pressure on it produced bile at the ampulla. The mucosa was not remarkable. The extrahepatic ducts were normal.

Spleen: The spleen was approximately twice the normal size and weighed 450 Gm. The capsule was wrinkled and blue. The spleen was soft in consistency. On cut section the malpighian corpuscles were not distinct; little of the pulp could be removed by scraping.

Bone Marrow: A portion of the femur was removed and showed relatively firm red hyperplastic marrow replacing most of the fat normally present in the medullary cavity.

Other Organs: The gastro-intestinal tract, pancreas, kidneys, aorta, thyroid, thymus, pituitary, adrenals, testes and brain showed no abnormalities.

Microscopic Postmortem Examination.—Liver: There were degenerative changes in the parenchymal cells of the liver. There were no unusual cellular collections in the portal spaces.

Spleen: The structure was greatly distorted, mainly in the pulp spaces, which were replaced by a relatively solid but somewhat reticulated stroma in which were many large undifferentiated cells, myeloblasts, eosinophilic myelocytes and small multinucleated cells. The malpighian corpuscles were scarcely recognizable.

Lymph Node: There was a partial loss of normal architecture, and the lymphoid follicles were almost completely obliterated. The sinuses were filled with undifferentiated cells similar to the cells described as present in the spleen.

Femoral Bone Marrow: The fat had been entirely replaced by a fairly dense reticulated structure which held many cells that were slightly larger than plasma cells but with an acidophilic cytoplasm. These cells were apparently differentiating into the myeloid series, for myeloid cells could be detected. Few cells of the erythropoietic series were visible. There were numerous small vascular channels in the framework. Megalokaryocytes were rare, but there was a fair number of giant cells, each with several nuclei, which might have been megalokaryocytes or degenerating cells of the myeloid series.

Costal and Sternal Bone Marrow: There was marked hyperplasia of leukopoietic cells and replacement of the little fat that is often present. There were a few megalokaryocytes like those present in the femoral marrow, but they were small and poorly formed. The predominant cell was large and polygonal, with a fairly dense cytoplasm and a deeply stained oval nucleus. Myelocytes could be distinguished, but there was little evidence of erythropoiesis. The marrow in general showed a proliferation of the reticular elements with the formation of a relatively dense framework. The appearances of the femoral, costal and sternal bone marrow were very similar; perhaps more marked alteration had occurred in the femoral marrow.

Postmortem Diagnosis: The diagnosis was myelogenous leukemia—clinically aleukemia, with involvement of the bone marrow, spleen and lymph nodes.

Comment.—During the three months this patient was under observation in the hospital he had persistent leukopenia and profound anemia without splenomegaly until shortly before death. Within the last twenty-four hours of life the tip of the spleen became barely palpable. During the early part of the patient's illness it was thought by some of the members of the staff that he might have an unusual form of pernicious anemia, but the number of erythrocytes failed to increase after the parenteral administration of liver extract. Other members of the staff favored the diagnosis of aplastic anemia. The occurrence of immature forms of leukocytes in the stained blood film and the finding of myeloid hyperplasia in the bone marrow of the sternum removed for biopsy were consistent with the diagnosis of aleukemic leukemia.

Case 3.—M. C., a white American man aged 47, entered the University of California Hospital on Feb. 18, 1936, complaining of weakness and dyspnea on exertion. He stated that he had felt well until early in December 1935, when he noticed progressive ease of fatigability, dyspnea and occasional cardiac palpitation. His physician told him his liver was enlarged and that he was anemic. For this condition the patient was given injections of liver extract, but there was no relief of symptoms. When the patient was admitted to the hospital it was learned that he had been employed as a member of a steel construction crew, but he denied knowledge of exposure to lead or fumes of benzene. There was no history of recent infection. He had subsisted on a well balanced diet.

Physical Examination.—The patient appeared well developed and well nourished. There was marked pallor of the skin and mucous membranes, but no petechial hemorrhages were seen. Slight gingivitis was present, but there was no oozing of blood from the gums. There was no evidence of infection in the throat. No enlarged lymph nodes could be felt in the cervical or axillary regions, but a few slightly enlarged nodes were palpable in the inguinal regions. The edge of the liver was barely palpable, but the spleen could not be felt. The heart was not found to be enlarged on percussion, but a systolic murmur was audible over the mitral area.

Laboratory Data.—The blood count showed: hemoglobin, 24 per cent (3.4 Gm.) Sahli; erythrocytes, 870,000 per cubic millimeter; color index, 1.5, and leukocytes, 5,300 per cubic millimeter. The differential count showed: segmented polymorphonuclear leukocytes, 32 per cent; nonsegmented leukocytes, 12 per cent;

lymphocytes, 46 per cent; monocytes, 8 per cent, and myeloblasts, 2 per cent. There were 102 nucleated red blood cells per hundred white blood cells, and the icteric index was 10. An analysis of the gastric secretion revealed the presence of free hydrochloric acid. Fragility of the erythrocytes began at a concentration of 0.45 per cent of sodium chloride and was complete at 0.35 per cent. Roentgenograms of the teeth and chest failed to show any remarkable change. Roentgenograms of the abdomen did not demonstrate enlargement of the spleen. There was no evidence of an organic lesion in the gastro-intestinal tract on fluoroscopic examination after an opaque meal. Roentgenograms taken of the left humerus and femur did not show atrophy of any quality or quantity in either the cortical

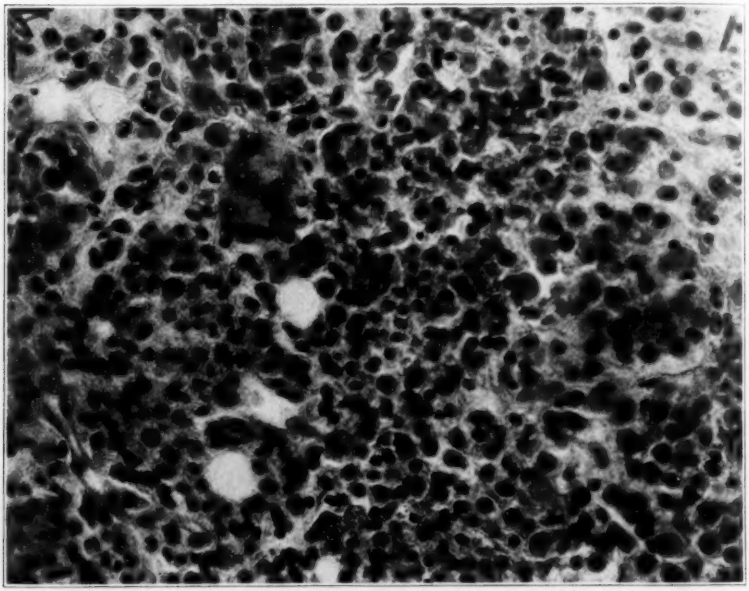

Fig. 2 (case 3).—Photomicrograph of sternal marrow removed for biopsy; × 300. There are large numbers of myeloblasts and large, round undifferentiated reticular cells.

or the medullary portions. The rose bengal dye was used in a test of hepatic function, which showed 58 per cent retention at the end of eight minutes and 28 per cent at the end of sixteen minutes (normal range).

Clinical Diagnosis.—The final clinical diagnosis was: aleukemic myelosis.

Biopsy of Sternal Marrow.—Examination of the sternal marrow revealed areas of bone surrounded by hyperplastic bone marrow. Large mononuclear cells of the myeloid series were numerous; their cytoplasm contained granules which stained eosinophilic, slightly acidophilic, neutrophilic or basophilic. Many myeloblasts also were present. Almost equally numerous were nucleated red blood cells or normoblasts. Few adult polymorphonuclear leukocytes were present. The diagnosis was involvement of the bone marrow consistent with aleukemic myelosis.

Course of the Illness.—The patient's general condition remained essentially the same as on entry. No change was observed after the administration of liver extract both by mouth and parenterally, cevitamic acid both by mouth and parenterally and the oral administration of reduced iron, 3.2 Gm. daily. On March 10, however, after a transfusion of 500 cc. of whole blood, slight improvement was noted. The blood count on March 16 showed: hemoglobin, 36 per cent; erythrocytes, 1,680,000, and leukocytes, 5,000. The differential count showed: segmented polymorphonuclear leukocytes, 34 per cent; nonsegmented leukocytes, 12 per cent, polymorphonuclear basophils, 2 per cent; lymphocytes, 32 per cent; monocytes, 2 per cent; myeloblasts, 14 per cent; promyelocytes, 2 per cent, and unclassified cells, 2 per cent. There were 60 nucleated red blood cells per hundred white blood cells.

The patient was discharged from the hospital to return home. Throughout the period of observation the temperature remained subnormal in the mornings but rose as high as 38.2 C. (100.8 F.) in the afternoons. Death occurred suddenly on April 10. Postmortem examination was refused.

Clinical Diagnosis.—The final clinical diagnosis was aleukemic myelosis.

Case 4.—H. W. C., a white American man aged 49 years, entered the University of California Hospital on Feb. 24, 1936, because of weakness, dyspnea on exertion and loss of weight. He was proud of the fact that he had not been ill since he was 18 years old, when he had typhoid. His illness started three months prior to entry, when he noted the gradual onset of weakness and mild dyspnea while climbing stairs. A physician told him that his hemoglobin value was 40 per cent and placed him on liver and iron therapy. He continued to fail in strength, and lost 25 pounds (11 Kg.) in weight.

Physical Examination.—The patient appeared well developed and well nourished, despite the history of loss of weight. There was pallor of the skin and mucous membranes. There was no demonstrable enlargement of the superficial lymph nodes. There was no evidence of infection about the gums or in the throat. Other than the presence of a soft blowing systolic murmur at the apex, examination of the heart showed nothing abnormal. Neither the spleen nor the liver was enlarged.

Laboratory Data.—The blood count showed: hemoglobin, 70 per cent (9.8 Gm.) Sahli; erythrocytes, 2,910,000 per cubic millimeter, leukocytes, 3,750 per cubic millimeter. The differential count showed: segmented polymorphonuclear leukocytes, 24 per cent; nonsegmented leukocytes, 14 per cent; eosinophils, 1 per cent; lymphocytes, 54 per cent, and monocytes, 7 per cent. The icteric index was 4.4. Hemolysis of red blood cells began at a concentration of 0.35 per cent sodium chloride and was complete at 0.25 per cent. Fluoroscopic examination and roentgenograms of the thoracic cavity and gastro-intestinal tract showed no signs of lesions, and no enlargement of the spleen could be demonstrated.

Course of the Illness.—The patient's temperature was normal except for a daily rise in the afternoon to 37.4 C. (99.3 F.). The anemia and leukopenia were not affected by the parenteral administration of liver extract or the oral administration of reduced iron. During the patient's stay in the hospital the blood count remained essentially the same, but an occasional myeloblast was observed in the stained blood films.

Biopsy of Sternal Bone Marrow.—The bone marrow showed a normal structure but was much more cellular than usual. Myeloid cells from the promyelocyte to the young leukocyte predominated and were numerous. Many mitotic figures were seen. Erythroblastic cells appeared in moderate number. The diagnosis was aleukemic myelosis.

Subsequent Course of the Illness.—The patient was discharged from the hospital on March 14, and he returned to the outpatient department on August 21, at which time his physical appearance was essentially the same. There was no apparent enlargement of the lymph nodes, liver or spleen. The blood count showed: hemoglobin, 65 per cent (9.2 Gm.) Sahli; erythrocytes, 1,700,000 per cubic millimeter; leukocytes, 3,600 per cubic millimeter, and platelets, 100,000. The differential count showed: segmented polymorphonuclear leukocytes, 1 per cent; nonsegmented leukocytes, 14 per cent; lymphocytes, 35 per cent; monocytes, 3 per cent; myelocytes, 7 per cent; myeloblasts, 30 per cent, and unclassified forms, 10 per cent. There were 7 nucleated red blood cells per hundred white blood cells.

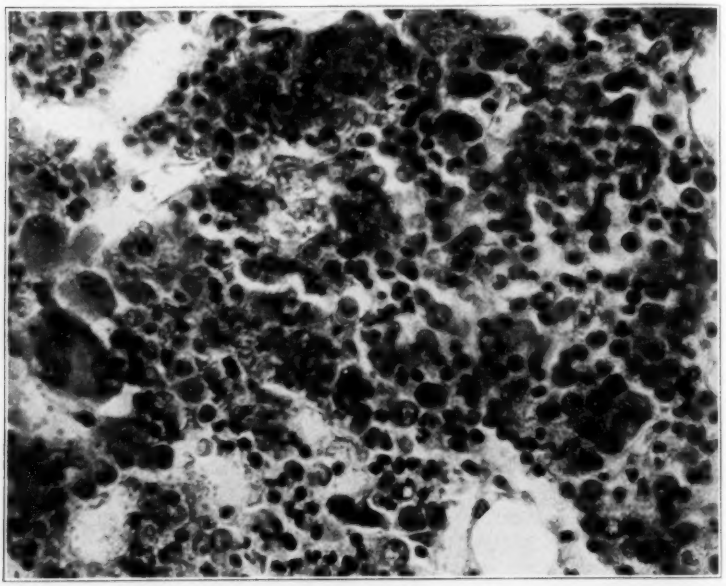

Fig. 3 (case 4).—Marked myeloid hyperplasia of the specimen of marrow removed from the sternum for biopsy; × 300. There are large numbers of myeloblasts and undifferentiated reticular cells.

Clinical Diagnosis.—The clinical diagnosis was aleukemic myelosis.

Case 5.—J. R., a white man aged 66, was admitted to the University of California Hospital on Nov. 30, 1936, complaining of weakness and dizziness of six weeks' duration. He was seen in the outpatient department on November 24, where the following diagnosis was made: (1) pernicious anemia and (2) bilateral hydrocele. This patient had been well until six weeks prior to entry into the hospital, when he noticed the gradual onset of weakness and dizziness. About November 1 he found it difficult to walk a short distance without support. During the week prior to entry he fainted three times. At the age of 16 he contracted gonorrhea, for which he received treatment; and he stated that at the age of 18 he had a chancre which subsided without treatment.

Physical Examination.—The patient appeared well developed and moderately well nourished. There was no evidence of infection in the skin, ears, nose or throat. There was marked caries of the teeth, and the gums showed moderate swelling and increased vascularity. The heart was not found to be enlarged on percussion. The blood pressure was 132 systolic and 74 diastolic. The edge of the liver was felt 2 cm. below the right costal margin and was smooth and slightly tender. The spleen was not felt on deep palpation. Lymph nodes averaging from 1 to 2 cm. in diameter were present in both inguinal regions. Elsewhere in the cervical and axillary regions the lymph nodes averaged less than 0.5 cm. in diameter.

Laboratory Data.—The blood count showed: hemoglobin, 28 per cent (3.92 Gm.) Sahli; erythrocytes, 1,180,000 per cubic millimeter, and leukocytes, 1,250 per cubic millimeter. The differential count was: segmented polymorphonuclear leukocytes, 16 per cent; nonsegmented leukocytes, 20 per cent; lymphocytes, 44 per cent; monocytes, 4 per cent; myelocytes, 4 per cent, and myeloblasts, 12 per cent. The color index was 1.18, the volume index 1.12, the mean corpuscular volume 101 and the mean corpuscular concentration 32 per cent. The platelets were moderately diminished in number, and the reticulocyte value was 0.8 per cent. The Wassermann and Kahn tests of the blood for syphilis gave positive reactions. There was an absence of free hydrochloric acid and pepsin from the gastric secretion after the administration of histamine.

Course of the Illness.—On December 5 the patient was given a transfusion of 500 cc. of whole blood, which was followed by relief of symptoms. There was no increase in the percentage of reticulocytes after the parenteral administration of liver extract.

While the patient was under observation in the hospital there was a gradual rise in the leukocyte count to a level of 4,000 cells per cubic millimeter. Associated with this was a shift in the differential formula to include higher percentages of immature forms. The patient was discharged from the hospital on December 30, at which time there were 30 per cent of myeloblasts in the stained blood film. It was of interest that many of these cells contained Auer bodies.

Clinical Diagnosis.—The diagnosis was aleukemic myelosis.

Biopsy of Sternal Marrow.—Sections showed markedly increased cellularity of the marrow and almost complete absence of fat cells. There were a large number of megakaryocytes scattered throughout the marrow. Many mature polymorphonuclear leukocytes were present. A large number of cells that were considered to be myeloblasts also was noted; among groups of these cells mitotic figures were noted. In addition to these cells there were many reticular cells. A few small areas of erythropoiesis were seen. It was concluded that the sternal marrow showed myeloid hyperplasia consistent with aleukemic myelosis.

Comment.—The presence of macrocytic anemia combined with achylia gastrica in this patient suggested the diagnosis of pernicious anemia. However, the erythrocytes and hemoglobin values failed to increase after the parenteral administration of liver extract. In the differential diagnosis it was thought possible, because of the slight generalized lymphadenopathy, that the abnormality of hematopoiesis resulted from reticulo-endotheliosis. Throughout the patient's stay in

the hospital there was a gradual shift to the left in the differential formula to include 30 per cent of myeloblasts. This evidence from the stained film supported the diagnosis of aleukemic myelosis.

SYMPTOMATOLOGY

The symptoms as they occurred in the patients are recorded in the histories. It is to be noted that the disease was insidious in onset. The most frequent complaint was that of gradually developing weakness extending over a period of from three to nine months. During the

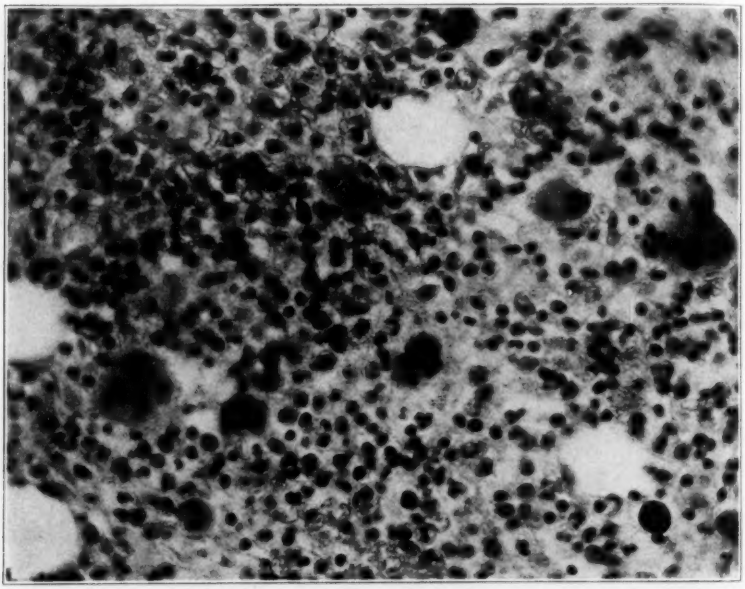

Fig. 4 (case 5).—Sternal marrow removed for biopsy; × 300. There is an increase in the number of immature myeloid forms and megakaryocytes.

course of the illness the patients became distressed by palpitation and dyspnea. There was little tendency toward remission or exacerbation of symptoms except when a sense of well-being followed transfusions of whole blood. Bleeding into the skin and from the mucous membranes occurred in two of the patients. It is worthy of note that all the patients were in a fair state of nutrition and did not have the cachectic appearance usually found in patients with neoplastic malignant growths or prolonged infection. In one patient there was moderate enlargement of the cervical lymph nodes, but in none was there clinical

evidence of enlargement of the spleen. The gums of one patient were swollen and bleeding, but there were no signs of gingivitis.

BLOOD PICTURE

From the accompanying table it will be seen that severe anemia was present in all the patients, the degree depending on the duration of illness and on whether or not a transfusion had been recently administered. The erythrocytes varied in number from a high level of 2,900,000 cells to as low as 500,000 cells per cubic millimeter, depending on the individual patient. The level of hemoglobin was reduced proportionately

Hematologic Data

Case	Date	Hemoglobin %	Hemoglobin Gm.	Red Blood Cells, Millions per Cu. Mm.	Platelets per Cu. Mm.	White Blood Cells, per Cu. Mm.	Polymorphonuclear Leukocytes, % Segmented	Polymorphonuclear Leukocytes, % Nonsegmented	Eosinophils, %	Lymphocytes, %	Monocytes, %	Myelocytes, %	Myeloblasts, %	Unclassified Cells, %	Nucleated Erythrocytes per 100 Leukocytes
1	2/ 2/32*	94	12.9	4.31	40,000	7,600	39	2	..	45	3	4	5	2	1
	2/25/32	50	7.0	1.78	.....	1,700	44	20	2	16	2	10	6	..	1
	3/ 3/32	65	8.9	2.30	30,000	1,350	18	23	4	25	4	18	6	2	2
2	7/20/33	55	7.7	2.86	.....	2,300	7	22	..	42	26	1	..	2	2
	9/ 5/33	43	5.9	2.46	.....	2,450	2	14	1	28	14	10	3	28	2
	10/24/33	10	1.4	0.50	40,000	980	8	28	..	16	12	20	16	..	..
3	2/18/36	24	3.4	0.87	.....	5,300	32	12	..	46	8	..	2	..	102
	3/16/36	36	5.1	1.68	.....	5,000	34	12	2	32	2	2	14	2	60
4	2/24/36	70	9.8	2.91	.....	3,750	24	14	1	54	7	..	..	..	..
	8/21/36	65	9.2	1.70	100,000	3,600	1	14	..	35	3	7	30	10	7
5	12/ 1/36	28	3.9	1.18	120,000	1,250	16	20	..	44	4	4	12	..	..
	12/17/36	32	4.5	1.76	304,000	3,150	5	18	2	33	2	4	30	6	2

* The patient received three transfusions of 500 cc. each of whole blood during the week prior to this examination.

less than that of the erythrocytes, so that the color index ranged from approximately 1 to 1.5. There was moderate to marked variation in the size and in the shape of the red blood cells. There were a great many large, round and definitely oval erythrocytes that were well filled with hemoglobin, and by contrast other cells appeared much smaller than normal. Nucleated red blood cells were noted in the stained films in all the cases, and in one instance there were as many as 102 per hundred white blood cells. The leukocyte count did not in any case exceed 5,300 cells per cubic millimeter, and the lowest count recorded was 980 per cubic millimeter.

In our cases, irrespective of the fact that leukocytosis was not present, it is to be noted that the qualitative changes in the differential formulas were similar to those typical of true leukemia. There was a shift to the left in the granulocytes to include myelocytes and myelo-

blasts. The immature forms comprised from 2 to 47 per cent of the total cells, which in the presence of leukopenia indicates an absolute increase of considerable degree.

There was a great reduction in the number of platelets in the blood of all our patients. This was accompanied in two cases with the usual manifestations of thrombocytopenic purpura, namely, spontaneous bleeding, prolongation of the time required for a clot to form and failure of the clot to retract properly.

BIOPSY OF BONE MARROW

Specimens of bone marrow from the sternum were obtained in four cases by the removal of a "button" of bone with a trephine having a 15 mm. bore. After removal, spread preparations were made on slides and cover slips for immediate staining and examination. Other pieces of marrow tissue were fixed in Zenker's fluid and at the appropriate time embedded in paraffin, sectioned and stained with hematoxylin and eosin. The two methods afforded an opportunity to study the finer cytologic structure together with the architectural arrangement of the marrow cells.

Photomicrographs are shown in figures 1 to 4 and correspond to case histories 2 to 5, respectively. In each of the sections the normal fatty tissue has been replaced by hyperplastic marrow. In general, the predominant type of cell contains a large vesicular nucelus in which may be seen masses of chromatin and in many cells 1 or more darkly stained nucleoli. The cytoplasm may vary in amount but usually consists of a narrow rim taking a light blue stain. These cells often appear in groups, and among them may be seen an occasional mitotic figure. When compared with "touch preparations" of fresh material on cover slips stained with Wright's stain, the cells may be identified as myeloblasts and early myelocytes. Comparatively few segmented forms are to be seen. Small groups of erythroblasts and normoblasts may be distinguished, but they play a less prominent rôle.

COMMENT

The leukemia in each of the five cases recorded here, it is believed, belonged to the myeloid group but differed from the usual form of the disease in that neither leukocytosis nor splenomegaly was present. These cases are reported because of their rarity and because of the difficulties encountered clinically in making a differential diagnosis from aplastic anemia or from certain conditions associated with a leukemoid blood picture, such as reticulo-endotheliosis, metastatic tumor nodules in the bone marrow,[8] osteosclerosis,[8] myelofibrosis[9] and abnormal

8. Mavros, A.: Aleukämische, besser "nichtleukämische" Myelose mit Osteosklerose, Folia haemat. **43**:323, 1931.

(Footnotes continued on next page)

leukopoiesis associated with infection.[10] For none of the patients, however, was there a history of chronic loss of blood, the presence of obvious infection or a demonstrable neoplastic process to account for the abnormal leukopoiesis.

It is to be emphasized that the diagnosis of this unusual manifestation of leukemia depends largely on the differential formula. For a patient with a greatly reduced total leukocyte count, a time-consuming and painstaking examination of the stained film is required in order to obtain a complete analysis of leukopoietic activity. In the cases reported here the diagnosis of aleukemic myelosis was considered tenable after the detection of myeloblasts, of a definite shift to the left in the leukocytes associated with severe anemia and of signs of regeneration of the erythrocytes.

Biopsy of marrow removed from the sternum affords an invaluable aid in establishing the diagnosis. Specimens of marrow showing a predominance of undifferentiated types of cells, many of which contain mitotic figures, packed solidly together to the exclusion of fat cells, enable the pathologist to render an opinion as to the nature of the hyperplasia of the marrow.

Since leukemia is considered a systemic disease, the usual structural changes are those of myeloid hyperplasia of the marrow associated with variable degrees of infiltration in the viscera, meninges and skin. The clinical manifestations, therefore, may be protean, depending on the degree of change occurring in different organs. It may be assumed, then, that myeloid metaplasia in the spleen may be of minimal amount, thus accounting for another unusual manifestation of leukemia.

SUMMARY

A description is given of five cases of leukemia in patients without leukocytosis and without splenomegaly. The clinical findings were those of severe anemia, thrombopenia and leukopenia with the presence of immature forms of leukocytes in the stained films of blood. Myeloid hyperplasia of the bone marrow consistent with leukemia was demonstrated by histologic examination of specimens removed from the sternum for biopsy.

Dr. C. L. Connor, of the Division of Pathology, gave us permission to use the postmortem and histologic data.

9. Mettier, S. R., and Rusk, G. Y.: Fibrosis of the Bone Marrow (Myelofibrosis) Associated with a Leukemoid Blood Picture, Am. J. Path. **13**:377 (May) 1937.

10. Krumbhaar, E. B.: Leukemoid Blood Pictures in Various Clinical Conditions, Am. J. M. Sc. **172**:519, 1926. Thompson, W. P.: Abnormalities in the White Blood Cell Response: Leukemoid, Atypical Leukemic and Leukopenic Blood Pictures, ibid. **182**:334, 1931.

INFLUENCE OF COPPER AND A LIVER FRACTION ON RETENTION OF IRON

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The influence of copper on the formation of hemoglobin is a problem which has not been completely solved, and the literature abounds in conflicting reports on the subject. Elvehjem [1] has recently summarized the work on the biologic significance of copper, and the reader is referred to this paper for a comprehensive review and bibliography. It has been found that in the experimental nutritional anemia of animals neither iron nor copper alone is effective in producing regeneration of hemoglobin, but when iron is given in combination with a small amount of copper a rapid increase in the hemoglobin content of the blood ensues. The work of Whipple [2] on experimental hemorrhagic anemia in dogs has not entirely confirmed these results. He found that in certain instances a combination of iron and copper was more beneficial than iron alone but that this was not consistently true. It is possible that a sufficient amount of copper may be obtained by these animals from unrecognized sources and as a contaminant of iron preparations to supply the small amount necessary for the formation of hemoglobin and so account for the beneficial effects apparently obtained from iron alone.

The effect of copper on the storage and retention of iron is no better understood than is its rôle in the formation of hemoglobin. It has been demonstrated in animals that copper does not increase the retention of iron when the two metals are given together,[3] but it does cause an

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From the Department of Internal Medicine, the State University of Iowa.

This work was begun in association with Dr. C. W. Baldridge, who died on Nov. 22, 1934.

1. Elvehjem, C. A.: The Biological Significance of Copper and Its Relation to Iron Metabolism, Physiol. Rev. **15**:471, 1935.

2. Robscheit-Robbins, F. S.; Elden, C. A.; Sperry, W. M., and Whipple, G. H.: Blood Regeneration in Severe Anemia: XII. Potent Influence of Inorganic Ash of Apricots, Liver, Kidney and Pineapple, J. Biol. Chem. **79**:563, 1928. Elden, C. A.; Sperry, W. M.; Robscheit-Robbins, S. F., and Whipple, G. H.: Blood Regeneration in Severe Anemia: XIII. Influence of Certain Copper Salts upon Hemoglobin Output, ibid. **79**:577, 1928.

3. Josephs, H. W.: Studies on Iron Metabolism and the Influence of Copper, J. Biol. Chem. **96**:559, 1932.

increased proportion of the iron to be used in the production of hemoglobin. When copper alone is given to an animal that has previously received iron, there is a reduction in the iron content of the liver.[4] These findings suggest that while copper does not greatly influence the retention of iron, it does affect its mobilization and utilization.[5]

Excellent clinical results have been reported in the treatment of hypochromic anemia by the administration of a combination of iron and copper,[6] although other investigators have felt that this combination has no advantage over iron alone. It has been assumed that sufficient copper is present in the food and as a contaminant of iron-containing drugs to supply all that is needed for hemoglobin regeneration, but Bethell [7] reported that the efficacy of iron in hypochromic anemia was not lessened when it was given in the form of reduced iron and in conjunction with a diet low in copper. Although Elvehjem concluded that "copper is necessary as a supplement to iron in hemoglobin formation in red-blooded animals," the evidence seems to favor the view that sufficient amounts are obtained from ordinary sources, so that additional copper medication is unnecessary.

Equally confusing are the reports on the effect of liver and liver extract in hypochromic anemias. Whipple [8] has shown that liver and certain liver fractions are potent in producing a regeneration of hemoglobin in the dog but that supplementing this liver fraction with iron may still further increase the output of hemoglobin. It has been shown also that a combination of liver and iron is effective in the nutritional anemia of rats.[9] Keefer [10] has demonstrated that this combination is more effective than iron alone in some cases of hypochromic anemia, while in others the addition of liver is unnecessary. Cheney and

4. Elvehjem, C. A., and Sherman, W. C.: The Action of Copper in Iron Metabolism, J. Biol. Chem. **98**:309, 1932.

5. Cook, S. F., and Spilles, N. M.: Some Factors Regulating the Utilization of Splenic Iron, Am. J. Physiol. **98**:626, 1931.

6. Mills, E. S.: The Treatment of Idiopathic (Hypochromic) Anemia with Iron and Copper, Canad. M. A. J. **22**:175, 1930. Elvehjem.[1]

7. Bethell, F. H.; Goldhamer, S. M.; Isaacs, R., and Sturgis, C. C.: The Diagnosis and Treatment of the Iron-Deficiency Anemias, J. A. M. A. **103**:797 (Sept. 15) 1934.

8. Whipple, G. H.; Robscheit-Robbins, F. S., and Walden, G. B.: Blood Regeneration in Severe Anemia: XXI. A Liver Fraction Potent in Anemia Due to Hemorrhage, Am. J. M. Sc. **179**:628, 1930.

9. Hart, E. B.; Steenbock, H.; Waddell, J., and Elvehjem, C. A.: Iron in Nutrition: VII. Copper as a Supplement to Iron for Hemoglobin Building in the Rat, J. Biol. Chem. **77**:797, 1928.

10. Keefer, C. S., and Yang, C. S.: The Treatment for Secondary Anemia Arch. Int. Med. **48**:537 (Oct.) 1931; The Value of Liver and Iron in the Treatment of Secondary Anemia, J. A. M. A. **93**:575 (Aug. 24) 1929.

Niemand [11] recommended the combination in cases of posthemorrhagic anemia, but Powers and Murphy [12] said they believed the addition of liver is of no value, and Bethell [7] found that simple preparations of iron gave results that compared favorably with the results obtained with iron in combination with other substances. Studies of the iron balance [13] in infants show that breast milk facilitates the absorption of iron from the gastro-intestinal tract, that copper does not influence the iron balance but that liver extract causes an improvement in the retention of iron. The present investigation was undertaken to obtain further information on these problems as they are applied to hypochromic anemia of adults.

The essential clinical and hematologic data for each patient are given in tables 1 and 2. The methods of study were the same as those employed in

TABLE 1.—*Clinical Features*

Patient	Age	Sex	Diagnosis	Clinical Features
1	26	F	Idiopathic hypochromic anemia	No history of unusual loss of blood; adequate diet; palpable spleen; koilonychia; free hydrochloric acid in gastric contents only after administration of histamine; idiopathic epilepsy
2	48	F	Hypochromic anemia; hemorrhage	Chronic bronchitis of four years' duration; mild atrophic arthritis; no abnormal loss of blood
3	48	F	Hypochromic anemia; hemorrhage	Gastric distress for two years with roentgenographic evidence of gastric ulcer; profuse menstruation
4	34	F	Hypochromic anemia; hemorrhage	Menorrhagia
5	34	F	Idiopathic hypochromic anemia	No history of unusual loss of blood; had bruised easily for years; koilonychia present for seven years; dysphagia
6	40	F	Hypochromic anemia	Minimal pulmonary tuberculosis in apex of left lung
7	41	F	Idiopathic hypochromic anemia	No history of unusual loss of blood; palpable spleen; no pregnancies; achlorhydria; one sister had anemia
8	23	F	Hypochromic anemia; hemorrhage	Had one child and three miscarriages; was pale and lost considerable blood with each pregnancy; menses irregular
9	40	F	Idiopathic hypochromic anemia	No unusual loss of blood; dysphagia; hypochlorhydria; ten pregnancies; was pale and weak with each; did not regain strength after last pregnancy three years previously
10	45	F	Hypochromic anemia; hemorrhage	Menorrhagia

previously reported determinations of iron balance,[14] and the same diets were used throughout. The patients were placed on this diet for a three day period of adjustment before the balance studies were begun, and this was followed by

11. Cheney, G., and Niemand, F.: The Treatment of Secondary Anemia with "Secondary Anemia Liver Extract" and Iron, Am. J. M. Sc. **184**:314, 1932.

12. Powers, J. H., and Murphy, W. P.: The Treatment of Secondary Anemia, J. A. M. A. **96**:504 (Feb. 14) 1931.

13. Maurer, S.; Greengard, J.; Curtiss, W. F., and Kluver, C.: The Effect of Small Quantities of Breast Milk, Liver Extract, Iron and Copper, Respectively and in Combinations, upon the Iron Balance of Artificially Fed Infants, J. Pediat. **4**:356, 1934.

14. (*a*) Fowler, W. M.; Barer, A. P., and Spielhagen, G. F.: Retention and Utilization of Small Amounts of Orally Administered Iron, Arch. Int. Med. **59**: 1024 (June) 1937. (*b*) Fowler, W. M., and Barer, A. P.: Retention and Utilization of Orally Administered Iron, ibid. **59**:561 (April) 1937.

TABLE 2.—*Hematologic and Laboratory Data*

Patient	Hemoglobin, Percentage	Hematocrit Reading, Percentage	Erythrocytes, Percentage	Color Index	Volume Index	Saturation Index	Gastric Acidity	Basal Metabolic Rate
1	46	68	106	0.43	0.64	0.67	Low	+13
2	58	79	89	0.65	0.88	0.73	Low	+ 8
3	31	49	68	0.45	0.72	0.63	Low	— 2
4	43	65	74	0.58	0.87	0.66	Normal	—17
5	39	57	89	0.43	0.64	0.68	.....	— 8
6	34	51	82	0.41	0.62	0.66	0	—16
7	39	65	88	0.44	0.73	0.60	0	....
8	53	68	78	0.67	0.87	0.77	Low	....
9	43	69	79	0.54	0.87	0.62	Low	....
10	16	31	48	0.33	0.64	0.51	0	....

TABLE 3.—*Detailed Results of Balance Studies*

		Nitrogen, Mg. per Day			Phosphorus, Mg. per Day			Iron, Mg. per Day			Erythrocytes, Millions per Cu. Mm.	Hemoglobin, Gm. per 100 Cc.
Patient	Period	Intake	Excretion	Balance	Intake	Excretion	Balance	Intake	Excretion	Balance		
1	1	10.57	11.63	—1.06	1.59	1.76	—0.17	12.3	10.6	+ 1.7	5.29	6.525
	2	11.48	11.39	+0.00	1.74	2.27	—0.53	246.5	206.0	+ 40.5	4.39	6.545
	3	10.48	10.79	+0.69	1.74	2.29	—0.55	246.4	244.9	+ 1.5	4.79	6.735
	4	9.95	9.16	+0.79	1.44	2.09	—0.65	217.0	285.9	— 68.9	5.35	7.275
	5*	10.10	10.77	—0.67	1.43	1.38	+0.06	517.7	241.0	+276.7	5.55	8.570
2	1	9.80	7.74	+2.06	1.44	1.02	+0.42	12.0	7.3	+ 4.7	4.44	8.150
	2	9.93	7.11	+2.82	1.44	1.19	+0.25	217.1	87.4	+129.7	4.28	7.275
	3	9.91	6.95	+2.96	1.44	1.00	+0.44	221.7	173.9	+ 47.8	4.82	8.230
	4	10.59	8.31	+2.28	1.49	1.12	+0.37	260.8	337.2	— 76.4	5.03	8.340
	5	10.79	8.88	+1.91	1.50	1.05	+0.45	260.9	187.2	+ 73.7	4.92	9.770
3	1	9.80	9.62	+0.18	1.44	1.22	+0.22	12.0	14.3	— 2.3	3.40	4.360
	2	9.93	7.40	+2.53	1.44	1.14	+0.30	217.1	231.1	— 14.0	3.92	4.360
	3	9.92	6.66	+3.26	1.44	0.73	+0.71	216.9	130.9	+ 86.0	4.10	6.385
	4	10.59	10.27	+0.32	1.49	0.97	+0.52	260.8	341.1	— 80.3	4.35	7.190
	5	10.79	9.25	+1.54	1.50	1.07	+0.43	260.9	218.4	+ 42.5	5.01	7.800
4	1	9.80	10.91	—1.11	1.44	1.25	+0.19	12.0	9.8	+ 2.2	3.69	6.200
	2	9.93	9.27	+0.66	1.44	1.12	+0.32	217.1	160.7	+ 56.4	4.01	6.805
	3	9.90	8.22	+1.68	1.44	0.79	+0.65	230.5	173.9	+ 56.6	3.88	7.100
	4	10.59	9.01	+1.58	1.49	1.34	+0.15	260.8	364.0	—103.2	3.98	8.115
	5	10.79	9.10	+1.69	1.50	1.01	+0.49	260.9	237.2	+ 23.7	4.25	8.680
5	1	9.78	9.46	+0.32	1.44	1.14	+0.30	11.9	13.3	— 1.4	4.47	5.595
	2	11.08	8.80	+2.28	1.44	0.96	+0.48	426.7	117.0	+309.7	4.48	5.855
	3	10.78	9.29	+1.49	1.44	1.55	—0.11	426.6	137.2	+289.4	4.85	6.455
6	1	9.78	11.87	—2.09	1.44	1.26	—0.18	11.9	21.7	— 9.8	4.10	4.785
	2	10.08	10.21	—0.12	1.44	1.48	—0.04	517.7	235.1	+282.6	4.37	5.595
	3	10.08	10.13	—0.05	1.44	1.34	+0.10	517.7	394.1	+123.6	4.55	5.645
	4	10.08	10.03	+0.05	1.44	1.35	+0.09	517.7	234.2	+283.5	4.67	7.450
	5	10.08	9.60	+0.48	1.44	1.65	—0.21	517.7	198.9	+318.8	4.71	8.680
	6	10.08	9.52	+0.56	1.44	1.58	—0.14	517.7	187.3	+330.4	4.99	10.370
	7	10.08	10.06	+0.02	1.44	1.66	—0.22	517.7	397.4	+120.3	5.17	9.470
	8†	10.08	11.29	—1.21	1.44	1.14	+0.30	517.7	420.6	+ 97.1	4.71	11.570
	9	10.08	12.56	—2.48	1.44	1.52	—0.08	517.7	617.2	— 99.5	4.74	12.200
7	1	9.79	9.77	+0.02	1.45	0.97	+0.48	12.0	40.8	— 28.8	4.41	5.595
	2	11.03	9.11	+1.92	1.47	1.22	+0.25	281.8	221.1	+ 60.7	4.34	5.595
	3	11.04	7.44	+3.60	1.48	1.09	+0.39	281.9	260.6	+ 21.3	4.45	5.823
	4	10.88	7.28	+3.60	1.48	0.98	+0.50	275.9	197.5	+ 78.4	4.50	6.310
8	1	11.03	8.73	+2.30	1.63	1.23	+0.40	12.6	11.2	+ 1.4	3.92	7.540
	2	13.49	10.06	+3.43	1.84	1.20	+0.64	283.3	200.7	+ 82.6	3.87	7.800
	3	13.49	10.61	+2.88	1.84	1.25	+0.59	283.2	227.2	+ 56.0	4.23	9.020
	4	13.51	10.39	+3.12	1.84	1.13	+0.71	283.3	143.2	+140.1	3.93	8.905
	5	13.48	12.08	+1.40	1.83	1.55	+0.28	283.4	352.8	— 69.4	4.38	8.680
9	1	9.78	9.38	+0.40	1.44	1.23	+0.21	11.9	24.4	— 12.5	3.98	6.140
	2	10.88	10.37	+0.51	1.48	1.23	+0.25	273.9	148.6	+125.3	3.98	6.650
	3	10.88	8.71	+2.17	1.48	0.92	+0.56	273.9	167.4	+106.5	4.30	8.115
	4	11.69	7.28	+4.41	1.63	0.87	+0.76	274.4	163.9	+110.5	4.92	8.570
	5	11.35	9.05	+2.30	1.66	1.14	+0.52	274.7	163.8	+110.9	4.14	9.470
	6	11.32	10.52	+0.80	1.68	1.03	+0.65	274.7	300.3	— 25.6	4.17	10.070
10	1	9.78	8.67	+1.11	1.44	1.20	+0.24	11.9	8.9	+ 3.0	2.40	2.230
	2	10.79	9.50	+1.29	1.48	1.04	+0.44	275.9	192.2	+ 83.7	2.33	2.610
	3	11.04	9.11	+1.93	1.48	1.33	+0.15	263.9	236.3	+ 27.6	2.96	3.395
	4	11.04	9.71	+1.33	1.48	1.73	—0.25	263.9	227.3	+ 36.6	3.40	5.200
	5	11.04	9.35	+1.69	1.48	1.46	+0.02	263.9	220.4	+ 43.5	3.95	6.385
	6	11.04	10.03	+1.01	1.48	1.44	+0.04	263.9	170.3	+ 93.6	3.77	6.595
	7‡	10.79	12.03	—1.24	1.48	1.22	+0.26	269.9	373.8	—103.9	5.22	10.940
	8	10.79	11.16	—0.37	1.48	1.24	+0.24	269.9	203.8	+ 66.1	5.23	11.360

* Iron and ammonium citrates given without copper.
† Sixty-six day interval between periods 7 and 8; medication continued.
‡ Sixty-five day interval between periods 6 and 7; medication continued.

a six day control period, during which the iron ingested was obtained from the food alone. The subsequent balance periods were of six days' duration, and the results given in the tables show the average daily retention for that six day period. Patients 1 to 4 received 60 cc. of an elixir of a copper and iron compound three times daily, which on analysis yielded from 217 to 260 mg. of iron per day. Patient 1 during a fourth balance period received 3 Gm. of iron and ammonium citrates per day with no copper. Patients 5 and 6 received an aqueous solution of iron and ammonium citrates and cupric sulfate of such strength that each 60 cc. contained 1.5 mg. of cupric sulfate and 1 Gm. of iron and ammonium citrates, which supplied approximately 500 mg. of iron per day. Patients 7 to 10 received iron plus a liver fraction.[15] This, on analysis, yielded from 263.9 to 283.4 mg. of iron per day. The complete results of the balance studies are given in table 3, and a summary of the retention of iron by periods is given in table 4. The iron content of the copper and iron compound was in the form of ferric citrate while the iron in the liver preparation was iron and ammonium citrates.

TABLE 4.—*Average Daily Iron Balances in Milligrams*

Patient	Control Period	Period 1	Period 2	Period 3	Period 4	Period 5	Period 6	Period 7	Period 8	Total Iron Balance
1	+ 1.7	+ 40.5	+ 1.5	— 68.9	.....	.....	.....	.....	.....	— 162.0
2	+ 4.7	+129.7	+ 47.8	— 76.4	+ 73.7	.....	.....	.....	.....	1,048.7
3	— 2.3	— 14.0	+ 86.0	— 80.3	+ 42.5	.....	.....	.....	.....	205.0
4	+ 2.2	+ 56.4	+ 56.6	—103.2	+ 23.7	.....	.....	.....	.....	201.1
5	— 1.4	+309.7	+289.4	.....	.....	.....	.....	.....	.....	3,594.3
6	— 9.8	+282.6	+123.6	+283.5	+318.8	+330.4	+120.3*	+97.1	—99.5	8,740.8
7	—28.5†	+ 60.7	+ 21.3	+ 78.4	.....	.....	.....	.....	.....	962.6
8	+ 1.4	+ 82.6	+ 56.0	+140.1	— 69.4	.....	.....	.....	.....	1,256.1
9	—12.5†	+125.3	+106.5	+110.5	+110.9	— 25.6	.....	.....	.....	2,506.6
10	+ 3.0	+ 83.7	+ 27.6	+ 36.6	+ 43.5	+ 93.6‡	—103.9	+66.1	.....	1,483.0

* Sixty-six day interval between periods 6 and 7 with continuous medication.
† Menstrual loss of blood.
‡ Sixty-five day interval between periods 5 and 6 with continuous medication.

COPPER

The first four patients received the iron and copper preparation in such amounts that the intake of iron ranged from 216.9 to 260.9 mg. per day and the iron balances ranged from — 14 to + 129.7 mg. per day during the first two balance periods. The average daily iron balance of the four patients for these two periods was + 53.1 and + 47.9 mg., respectively, which is slightly larger than was found in a previously reported group of patients receiving from 170.5 to 233.2 mg. of iron per day without copper.[14a] During the third balance period all the patients showed a markedly negative iron balance, and in no other group of patients has such a consistent drop been noted. Three of the patients studied during a fourth period returned to a positive balance. The average daily iron balance and the percentage of the iron retained by each of the four patients during the entire period of observation are given in table 5, and it will be noted that the retention is distinctly less for those patients receiving copper than for those of the other groups.

15. The preparation used was lextron.

Patient 1, in a fourth balance period, not recorded in table 4, received 517.7 mg. of iron per day with no copper and retained 276.7 mg. daily. This is comparable to the amount retained by patients previously reported on who received a similar amount of iron alone.[14b]

Patients 5 and 6 received an aqueous solution of iron and ammonium citrates yielding 426 mg. (patient 5) and 517 mg. (patient 6) of iron per day plus 1.5 mg. of cupric sulfate. The retention of iron was comparable to that which followed the administration of a similar amount of iron without additional copper.[14b]

Patient 1 was in negative iron balance throughout the first three periods of observation but showed a moderate increase in the hemoglobin content of the blood. The percentage of the administered iron which was retained by patients 2 to 4 varied from 3.4 to 18.1 per cent (table 6). This is decidedly less than was retained by the previous

TABLE 5.—*Retention of Iron*

Patient	Iron and Ammonium Citrates,* 170.6 to 183.9 mg. of Iron Daily		Copper Plus Iron,† 216.9 to 260.9 mg. of Iron Daily		Liver Extract Plus Iron, 263.9 to 283.4 mg. of Iron Daily	
	Average Daily Iron Retention, Mg.	Percentage of Iron Retained	Average Daily Iron Retention, Mg.	Percentage of Iron Retained	Average Daily Iron Retention, Mg.	Percentage of Iron Retained
1	55.2	30.5	0	0	53.4	19.0
2	43.2	23.6	43.6	18.1	52.3	18.4
3	42.6	23.2	8.5	3.5	85.5	31.1
4	82.8	45.1	8.3	3.4	35.3	13.2
5	44.7	27.1	....	....	....	....
Av.	53.7	29.9	15.1	6.2	55.3	20.4

* The data are taken from a preceding paper. Exclusive of patient 6, who received larger amounts of iron.

† Exclusive of patients 5 and 6, who received larger amounts of iron.

group of patients receiving no copper and a somewhat smaller amount of iron.[14a] The percentage retained by patients 5 and 6 was much greater and was comparable to that retained by those patients receiving a similar amount of iron without copper.[14b]

In studying the utilization of iron (table 6) we have again assumed that the blood volume of each patient was 5 liters and have calculated on this basis the approximate total increase in the hemoglobin content. The percentage of the iron used in the formation of hemoglobin varied from 2.5 to 9 per cent, with an average of 5.2 per cent for the first six patients (exclusive of patient 1). This should be compared with the 3.4 per cent utilization reported by Heath,[16] the 1.9 per cent utilization from large doses of iron [14b] and the 9.1 per cent utilization from moderate doses of iron without copper.[14a] This average utilization of the administered iron does not present the entire picture in patients 1, 3 and 4. It was noted that there was a definite increase in the hemo-

16. Heath, C. W.: Oral Administration of Iron in Hypochromic Anemia, Arch. Int. Med. **51**:459 (March) 1933.

globin content in patient 1, in spite of the fact that she apparently retained none of the administered iron. It will be noted also that the increase in hemoglobin in patients 3 and 4 accounted for more iron than was actually retained by the patients during the period of observation. Patient 3 retained 0.205 Gm. of iron but used approximately 0.516 Gm. in the building of hemoglobin; patient 4 retained 0.201 Gm. but used 0.372 Gm. in the formation of hemoglobin. This excess of hemoglobin iron above the retained iron must be obtained from the reserve supplies of the body and is in keeping with previous experimental work showing that copper aids in the mobilization and utilization of iron without actually increasing the absorption.[17] Heath, giving iron parenterally but without additional copper, also noted a utilization of over 100 per cent in certain cases. In patients 5 and 6 only 3 and 9 per cent, respectively, of the retained iron was utilized, which is a no greater retention than when iron in the same amount is given alone.

TABLE 6.—*Retention and Utilization of Iron*

Patient	Total Iron Intake, Gm.	Total Iron Retained, Gm.	Original Hemoglobin Value, Gm. per 100 Cc.	Average Daily Increase in Hemoglobin, Gm. per 100 Cc.	Total Increase in Hemoglobin, Gm. per 100 Cc.	Iron, Percentage Retained	Iron Percentage Utilized in Hemoglobin
1	4.259	—0.162	6.52	0.041	37.5	0.0	...
2	5.762	1.049	8.15	0.067	81.0	18.1	4.2
3	5.733	0.205	4.36	0.143	172.0	3.5	9.0
4	5.816	0.201	6.20	0.103	124.0	3.4	6.3
5	5.119	3.594	5.59	0.071	43.0	70.2	2.5
6	24.849	8.741	4.78	0.110	265.7	35.1	3.2
7	5.038	0.962	5.59	0.040	36.0	19.0	2.1
8	6.799	1.256	7.54	0.047	57.0	18.4	2.5
9	8.220	2.566	6.14	0.131	196.5	31.1	7.1
10	11.228	1.483	2.23	0.114	239.2	13.2	6.3

LIVER FRACTION

The effect of a liver fraction on the retention of iron is illustrated by patients 7 to 10. These patients received the liver preparation in such amounts that the intake of iron ranged from 263.9 to 283.4 mg. per day. The amount retained is shown in table 4. It will be noted that in patients 8 to 10 there was one period in which there was a decidedly negative iron balance but this did not come in the same balance period for the different patients as was true for the patients receiving copper. In table 5 will be found the average daily retention of iron of each patient, and this may be compared to the retention in other groups of patients receiving similar amounts of iron. It will be noted that the amount of iron retained is almost the same in those receiving liver and iron as in those receiving a smaller amount of iron alone and that both of these groups retained much more iron than

17. Elvehjem,[4] Cook and Spilles,[5] Mills.[6]

did those patients receiving additional copper. The percentage of iron retained was larger in the patients receiving liver than in those who received copper, but it was smaller than in those receiving iron alone. The percentage of the iron utilized in the formation of hemoglobin was 4.5 per cent.

COMMENT

The results of these experiments indicate that when iron is given in moderate amounts (217 to 260 mg. per day), the addition of copper causes a diminished retention of iron. In spite of the small amount of iron retained, there is a satisfactory hemoglobin response, which in three of the four patients accounted for more iron than was retained by the body. This suggests that copper in some way aids in the utilization and mobilization of the available iron already stored in the body. When larger amounts of iron are administered in combination with copper (patients 5 and 6), there is no appreciable change in the retention or utilization of iron as compared to that in patients [14b] receiving a similar amount of iron alone.

The combination of iron and a liver fraction produced a retention of iron which was slightly less than that in patients receiving iron alone. The percentage of iron retained dropped from 29.9 to 20.4 with the addition of liver. These results indicate that both the liver fraction and the copper diminish the amount of iron retained by the body but that the greater decrease is caused by copper.

The average daily increase in the hemoglobin content was 0.111 Gm. per hundred cubic centimeters of blood with iron alone, 0.089 Gm. with copper and iron and 0.082 Gm. with a combination of a liver fraction and iron. A somewhat smaller amount of iron was being administered in the first instance. These experiments were designed primarily for the study of the retention of iron, and results of the formation of hemoglobin based on so small a series of patients does not justify extensive and final conclusions. They suggest, however, that the addition of copper or a liver fraction does not increase the rapidity of the formation of hemoglobin in hypochromic anemias which are essentially post-hemorrhagic in origin.

SUMMARY

Iron balances were determined for ten patients with hypochromic anemia in order to study the effect of copper and liver extract on the retention of iron.

When iron was given in moderate amounts, the addition of copper led to a diminished retention but an increased utilization of iron. When the iron was administered in large doses, the effect of copper was negligible. Liver extract caused a slightly reduced retention of iron.

The increase in hemoglobin in this series of patients was no more rapid with the addition of copper or liver extract than with iron alone.

DIVERTICULUM OF THE PERICARDIUM

FURTHER DATA SHOWING PRESENCE OF EXTRATHORACIC ABSCESS

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In the January 1937 issue of the ARCHIVES was given a detailed report [1] of a patient with a mass which was considered to be a pericardial diverticulum. Further data are presented here:

The patient had been in good health and had been working as a night watchman. He was readmitted to the Lakeside Hospital in January 1937. Ten days previously there had been hematemesis of about 500 cc., and he had remained in bed at home for a week. Three days before admission to the hospital he had a head cold, and the night before entry fever, shortness of breath and pain in the chest were noted. When admitted to the hospital he had a temperature of 40 C. (104 F.). There were râles at the base of each lung. Cultures of the blood and sputum contained type II pneumococci. The patient died the next day.

Postmortem Examination (Dr. Alan R. Moritz).—An autopsy was performed on January 22, four hours after the patient's death. The pathologic diagnoses were:

Chronic tuberculous pericarditis, with anterior extrathoracic pseudodiverticulum (communicating abscess) of the pericardium
Chronic cardiac compression, with extreme cardiac deformity
Generalized chronic passive hyperemia
Bronchopneumonia of the lower lobe of each lung
Extensive fibrous pleural adhesions on the right
Chronic peptic ulcer in the lesser curvature of the stomach, near the pylorus
Hemorrhoids

The fluctuant area beneath the skin of the right side of the thorax measured 4 cm. in diameter, and its apex was elevated about 2.5 cm. above the level of the adjacent wall of the chest (fig. 1). On section an encapsulated abscess, containing about 5 cc. of thin cloudy brown fluid, was noted beneath the origin of the pectoralis major muscle. The capsule was thick and was comprised of a dense lamella of fibrous connective tissue in the outer portion of which bundles of skeletal muscle were incorporated. The lining of the abscess was irregularly granular and was roughened by friable masses of necrotic tissue and organized exudate. The cartilage of the fourth rib had been destroyed, and through the defect the abscess communicated by means of a narrow sinus tract with an intra-

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1. Cushing, E. H.: Diverticulum of the Pericardium, Arch. Int. Med. **59**:56 (Jan.) 1937.

pericardial abscess (fig. 2 *A*). This abscess lay over the anterior basal portion of the heart, measured 15 cm. in its greatest diameter and contained about 350 cc. of thin cloudy brown fluid, in which were a number of delicate yellow crystals. Near the ostium of the sinus in the pericardial abscess was a polypoid mass of granulation tissue that could have acted as a valve, permitting the entrance of fluid or gas into, but interfering with its passage out of, the pericardium.

Fig. 1.—The thoracic contents and the extrathoracic abscess (pseudodiverticulum of the pericardium) viewed from the right side. The right pleural cavity and the mediastinum have been obliterated by dense fibrous adhesions.

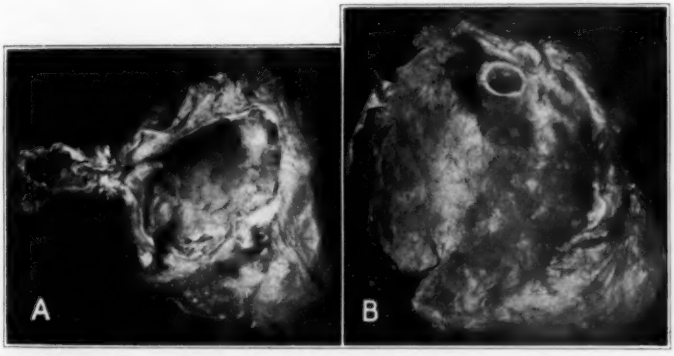

Fig. 2.—*A*, a view of the intrapericardial abscess, the sinus tract and the communicating extrathoracic abscess. *B*, all the parietal and most of the visceral pericardium has been dissected from the heart. The amount of compression of the heart is indicated by the concave deformity of the base, with extreme flattening of the auricles and the pulmonary conus.

Posteriorly, laterally and inferiorly the pericardial sac was obliterated by dense fibrous adhesions in which were many thick plaques of calcareous material. The inner surfaces of these plaques were irregularly nodular, with extension into

the underlying myocardium. An almost continuous band of calcareous material occupied the auriculoventricular sulcus.

Microscopic examination of the parietal pericardium and the wall of the communicating extrathoracic abscess revealed active solitary and active conglomerate tubercles. A section which included the transition between the parietal pericardium and the wall of the extrathoracic abscess showed an abrupt interruption of the orderly arranged lamellae of tissue of the parietal pericardium at the sinus. In their place the wall of the sinus and that of the extrathoracic abscess was comprised of a thick layer of organizing granulation tissue bearing no structural resemblance to the parietal pericardium, although being in direct continuity with it.

The heart, which was not enlarged, was greatly flattened in its anteroposterior axis, the flattening being most pronounced at the base (fig. 2 *B*). The auricular appendages were obliterated, and the auricles were converted into thin hollow plates, the anterior and posterior walls of which approximated each other closely. The entire heart was surrounded by dense fibrous connective tissue, and both the inferior and the superior vena cava were compressed by scar tissue. The superior vena cava had a rather sharp posterior angulation in addition to the compression. The endocardium, valves and coronary arteries showed no significant changes.

The lungs were the seat of edema and chronic passive hyperemia, and there were small moist gray consolidated patches in the lower lobe of each lung. The right pleural cavity was obliterated by fibrous adhesions. There was no gross or microscopic evidence of active or healed tuberculosis of the lungs or mediastinal lymph nodes.

The remainder of the postmortem examination disclosed no significant changes other than chronic passive hyperemia of the liver, spleen, kidneys and gastrointestinal mucosa, hemorrhoids and a chronic peptic ulcer near the pylorus.

COMMENT

The route by which the tubercle bacilli reached the pericardium was not disclosed by the autopsy. No active or healed lesions of tuberculosis were discovered except those in the pericardium and in the communicating extrathoracic abscess. The possibility of primary pulmonary tuberculosis was not excluded, however, as roentgenograms of the lungs and mediastinal lymph nodes were not made. Although the cartilage of the fourth rib had been destroyed, there was no osteomyelitis of the ribs or sternum. The exact mode by which the communicating abscess developed was not disclosed. It may have resulted from a tuberculous mediastinal abscess which perforated externally beneath the pectoralis major muscle and internally into the pericardium. It is equally possible that a pericardial abscess may have perforated anteriorly, with destruction of the overlying costal cartilage and extension beneath the pectoral muscle. In either event the extrathoracic abscess was not a true pericardial diverticulum. The parietal pericardium ended abruptly at the beginning of the sinus tract.

The polypoid mass of granulation tissue, just at the mouh of the opening of the sinus into the pericardial abscess, was of such a character and so located as to account for the fact that air could be forced from the extrathoracic abscess into the pericardium, but having entered the pericardium it became trapped there.

It is surprising that there was so little clinical evidence of cardiac compression. The deformity of the auricles was extreme, and the entire heart was encased in a thick, extensively calcified mass of scar tissue. Although there were no ascites, the chronic passive hyperemia of the abdominal viscera constituted postmortem evidence of long-standing circulatory failure that was not apparent in life.

CALCIFICATION OF MYOCARDIUM WITH BONE FORMATION

REPORT OF A CASE

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A review of the literature discloses that calcification of the myocardium with bone formation is an extremely rare phenomenon. We have been able to find reports of only five cases. While heteroplastic bone formation in sclerotic arteries has been made the subject of investigation by Buerger and Oppenheimer [1] and Harvey,[2] no study has been made of calcification of the myocardium with bone formation. We believe, however, that if calcification of the heart is extensive enough to be demonstrated roentgenographically, ossification should be considered at the same time.

Calcification of the myocardium without bone formation has been mentioned in the following reports:

Scholz,[3] in an extensive review of the literature up to 1924, referred to a total of thirty cases of myocardial calcification, adding a case of his own. He classified these into five groups:

1. Myocarditis, fourteen cases
2. Obliteration of coronary arteries, three cases
3. Sepsis, five cases
4. Calcium metastasis
   (*a*) Involving endocardium only, two cases
   (*b*) Combined with myocarditis, two cases
5. Direct extension from calcifying pericarditis, four cases

Diamond [4] collected reports of fourteen additional cases of myocardial calcification, reporting at that time the case of an infant born pre-

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From the Medical Service of Dr. Jacob N. Cohen, the Greenpoint Hospital.

1. Buerger, L., and Oppenheimer, A.: Bone Formation in Sclerotic Arteries, J. Exper. Med. **10**:354, 1908.

2. Harvey, W. H.: Experimental Bone-Formation in Arteries, J. M. Research **17**:25, 1907.

3. Scholz, T.: Calcification of the Heart: Its Roentgenologic Demonstration, Arch. Int. Med. **34**:32 (July) 1924.

4. Diamond, M.: Calcification of the Myocardium in a Premature Infant, Arch. Path. **14**:137 (Aug.) 1932.

maturely, at 26 weeks, who died of cardiac failure thirty minutes after birth. The necropsy showed marked involvement of the right auricle and scattered deposits of calcium in the walls of both ventricles. The epicardium and the coronary vessels were not involved.

Moore [5] cited the case of a white man aged 60 who, after having been hospitalized three times, was admitted a fourth time complaining of severe precordial pain and died six hours later. At autopsy the heart weighed 545 Gm., with the left ventricle bulging outward and containing a large deposit of calcium extending from the auriculoventricular groove downward to within 2 cm. of the apex.

Hirschboeck [6] reported the case of a laborer 60 years of age in whom myocardial calcification occurred subsequent to coronary occlusion. The calcification involved the area of cardiac muscle supplied normally by the occluded descending branch of the left coronary artery. The anterior surface of the left ventricle was attached by tough fibrous adhesions to the anterior surface of the pericardial sac. The adherent part of the left ventricle showed extensive calcification. The anterior branch of the left coronary artery was partly obliterated.

Cutler and Sosman [7] cited two cases in which there were extensive deposits of calcium in the myocardium, possibly caused by antecedent pericarditis and representing healed fibrinous pericarditis.

Microscopic evidence of bone formation in the calcified myocardium was not given in the aforementioned cases.

White [8] has stated the opinion that in rare cases actual bone is found in the myocardium instead of mere masses of lime salts.

From the earlier literature may be mentioned reports by Bordenave,[9] Simmons and Watson,[10] Burns [11] and Renauldin [12] of cases of bone formation in the myocardium.

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5. Moore, J. J.: Myocardial Calcification, Am. J. Roentgenol. **31**:766, 1934.

6. Hirschboeck, F. J.: Calcification of Myocardium Following Coronary Occlusion, Am. Heart J. **10**:264, 1934.

7. Cutler, E. C., and Sosman, M. C.: Calcification in the Heart and Pericardium, Am. J. Roentgenol. **12**:312, 1924.

8. White, Paul D.: Heart Disease, New York, The Macmillan Company, 1931.

9. Bordenave, M.: A Case of Ossification of the Heart, Mém. Acad. roy. de sc., Paris **1**:50, 1768; cited by Scholz.[3]

10. Simmons, S. F., and Watson, H.: A Case of Ossification of the Heart, Med. Communications, London **1**:228, 1783; cited by Scholz.[3]

11. Burns, Allan: Observations on Some of the Most Frequent and Important Diseases of the Heart, Edinburgh, Bryce & Co., 1809, p. 129.

12. Renauldin, M.: Mémoire sur le diagnostic de quelques maladies organiques du coeur, J. de méd., chir., pharm. **11**:254, 1806; cited by Corvisart, J. N.: Essai sur les maladies et les lésions organiques du coeur et des gros vaisseaux, ed. 3, Paris, Méquignon-Marvis, 1818.

Topham [13] observed a number of large sections of ossification in the myocardium of a man aged 61 years who suffered from cardiac insufficiency. He said:

> These hard and stony masses were found in the lines of the auricular-ventricular grooves. One, the larger, was 4 x 1 inch, widening up to 2 inches along the auricular-ventricular groove. In a similar position on the left side were 2 smaller fragments each about 1 x 1½ inches at their greatest diameters. The aorta and coronary arteries appeared normal. The heart was large, flabby and dilated. It had a firm fibrous covering which proved difficult to detach.

A patient with myocardial calcification with bone formation was observed at the Greenpoint Hospital, and since there is a paucity of material in the literature on this condition, we wish to present this report.

REPORT OF CASE

An Italian widower aged 64, a pedler, was admitted to the Greenpoint Hospital on Jan. 17, 1933, where he died on February 18. His chief complaint was of abdominal distention. His family history was essentially unimportant. His personal history showed that he had been an excessive wine drinker since the age of 30, imbibing two or three bottles daily. He smoked from eight to ten Italian cigars a day. He married at 18 and had twelve children. He had been a strenuous worker all his life. He had no knowledge of any cardiac lesion, rheumatism or venereal infection. His past history revealed no serious illness or operation. Eight months previously he noticed a gradual and progressive enlargement of the abdomen associated with shortness of breath on exertion. He was admitted on two occasions to a hospital at the onset of his illness, at which time abdominal paracentesis offered little relief because of the rapid reaccumulation of fluid. When he came under our observation his abdomen was tremendously enlarged, and the slightest exertion produced marked dyspnea. He had no cough, hemoptysis or precordial pain. He had lost a great deal of weight and had become progressively weaker. He was constipated and had marked nocturia.

The patient was poorly nourished, pale and dyspneic and appeared acutely ill. He was not cyanotic. Pterygium was present bilaterally. The supraclavicular depressions were marked. There was no venous engorgement or increased arterial pulsation in the neck. The trachea was not fixed. Retraction of the intercostal spaces in the lower portion of the right and left axillary regions was marked. Flatness on percussion with distant breathing was noted at the base of each lung. The maximal precordial impulse was observed in the fifth left intercostal space, 2 cm. outside the midclavicular line. Percussion revealed that the right and left cardiac borders together with the aortic arch were enlarged. The sounds were of fair quality and regular. A faint systolic murmur was audible over the apical and aortic areas. The aortic second sound was louder than the pulmonic second sound. No thrills or rubs were heard. The cardiac apex failed to shift with postural change. The abdomen was enormously distended, and shifting dulness together with a fluid wave was noted. The superficial veins in the lower portion of the chest and midabdominal area were markedly dilated. On compression they

13. Topham, J. A.: Bone Formations in the Heart, Brit. M. J. **2**:953 (Oct. 13) 1906.

filled from below. Edema was noted in the sacrum, scrotum, thighs and ankles. The extremities were warm and of good color and showed normal arterial pulsations. The external genitalia were normal. Rectal examination revealed slight enlargement of the prostate.

Abdominal paracentesis was performed on the day after the patient's admission to the hospital, and 5 gallons (23 liters) of yellowish opalescent fluid was obtained. This fluid proved to be a transudate. A smear of the fluid showed no malignant cells or organisms; a differential count showed 81 per cent polymorphonuclear cells and 19 per cent lymphocytes. After the paracentesis the liver was palpated 5 fingerbreaths below the right costal margin. It was firm and smooth. The spleen was not palpable. Peristalsis of the intestines at this time was visible. Subsequently, three additional paracenteses were performed because of the discomfort and dyspnea produced by the reaccumulation of ascitic fluid. A total of 14 gallons (64 liters) of ascitic fluid was obtained. After the second paracentesis, on the tenth day of hospitalization, the scleras became icteric. The skin was not jaundiced. The icteric index at this time was 38; a positive immediate direct van den Bergh reaction was obtained. Later the icteric index was 32.

The urine at all times showed the presence of bile and an increase in urobilinogen, together with a faint trace of albumin. The kidneys showed ability to concentrate. The blood count showed: erythrocytes, 3,050,000 and leukocytes, 12,000, with 73 per cent polymorphonuclears and 27 per cent lymphocytes. The hemoglobin value was 60 per cent. The total urea content of the blood was 35 mg. The Wassermann reaction was negative. The stools showed occult blood on numerous examinations.

The blood pressure never rose above 110 systolic; the diastolic pressure remained in the 70's. The temperature ranged between 99 and 101 F.; the pulse rate, between 90 and 100, and the respiratory rate, between 30 and 36.

During his stay in the hospital the patient grew progressively worse and refused to take nourishment. He became stuporous and lapsed into coma on February 17, with pulmonary edema. He died the next day.

Roentgenographic studies of the chest revealed unusual and interesting findings. The pulmonary fields showed an increase in hilar calcification but no infiltration or consolidation. Figure 1*A* shows the heart to be considerably enlarged in all diameters, with a large circular opacity in the lower aspect of the left field extending above the level of the diaphragm for about 2 inches (5 cm.); this opacity did not extend to the outer aspect of the pulmonary field; the periphery showed calcification. The left costophrenic sinus appeared clear. The transverse diameter of the aortic arch was increased. The mediastinal shadow was increased to the right in the middle and lower thirds; this was probably due to dilatation of the right auricle or the descending aorta. The right and left diaphragmatic domes were well outlined at the usual levels. An oblique view (fig. 1*B*) shows the calcified tissue to be anteriorly situated, thus excluding aortic aneurysm with calcification. Fluoroscopy and further roentgen examinations showed diffuse widening of the aorta and concentric hypertrophy of the left ventricle. Contractions in the region of the left ventricle were not observed on fluoroscopy. At no time was calcification thought to be present in the pericardium. In order to determine the extent of calcification more accurately, a roentgenogram of the excised heart was made (fig. 2). Here one may see the calcification involving the entire left ventricle, with a denser area containing bone. The electrocardiogram (fig. 3) revealed myocardial damage.

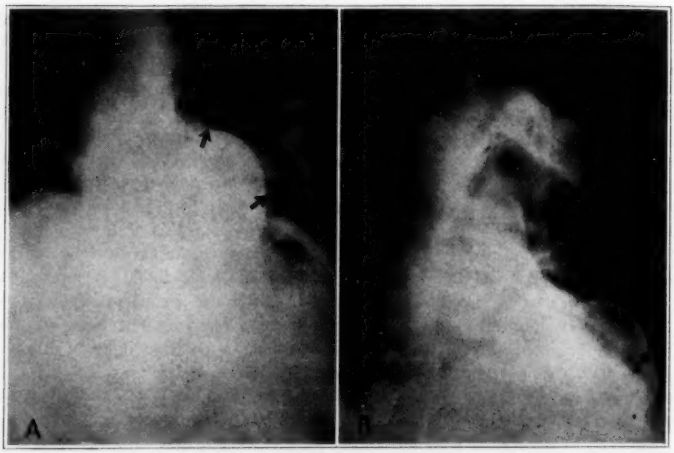

Fig. 1.—*A*, teleoroentgenogram showing the heart enlarged in all diameters, with a large circular opacity in the lower aspect of the left field. The periphery of this opacity showed calcification. *B*, an oblique view showing the calcified tissue to be anteriorly situated.

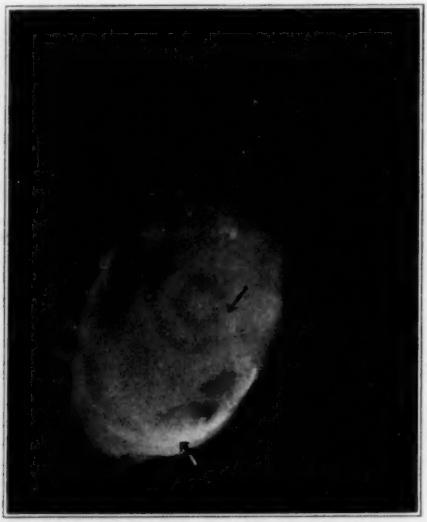

Fig. 2.—Roentgenogram of the excised heart, showing the extent of the bone formation in the left ventricle.

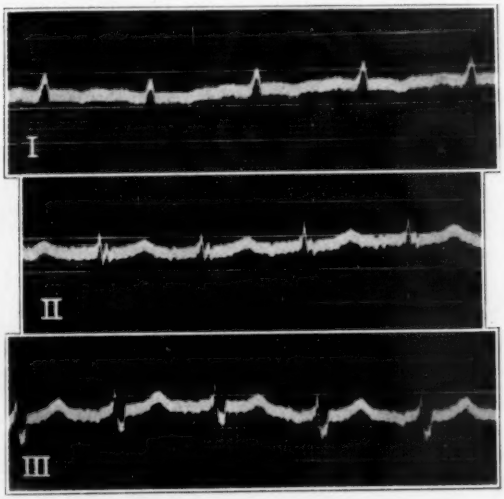

Fig. 3.—Electrocardiogram showing severe myocardial damage.

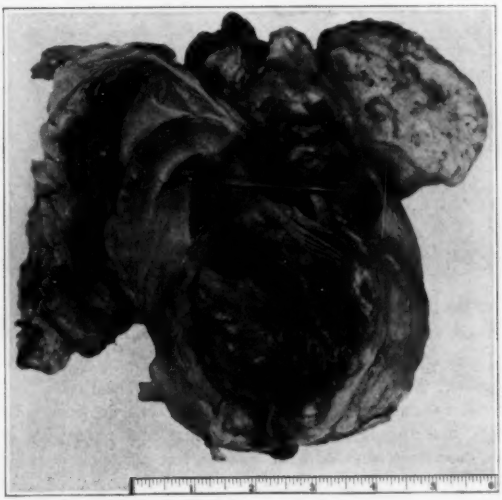

Fig. 4.—Left ventricle exposed, showing the oval shape and the thinning of the wall, with bone formation.

The anatomic diagnosis at postmortem examination was aneurysm of the left ventricle, severe sclerosis of the coronary vessels, myocardial calcification of the left ventricle, arteriosclerotic aortitis with ulcerations, anterior and lateral pericardial adhesions, pleural effusion with adhesions, fibrosis of the spleen and pancreas, severe cirrhosis and infarctions of the liver and passive congestion of the viscera. The kidneys showed evidence of chronic nephritis.

The heart weighed 800 Gm. and was enlarged to the right and left (fig. 4). The left ventricle was oval, and its distal three-fifths was transformed into a

Fig. 5.—Microscopic section (× 40) showing: *A*, fibrous tissue; *B*, marrow space containing fat globules, blood cells and capillaries, and *C*, osseous trabeculae.

large aneurysm about the size of a fist. The aneurysmal wall was thin, measuring from 2 to 8 mm. in thickness; it showed diffuse calcification, bulged outward and to the right and caused marked compression and narrowing of the right ventricle. The remaining myocardium of the left ventricle was about 2 cm. thick and pale; it showed diffuse areas of fibrosis. All the valves were apparently normal except for some fibrous thickening of the free edge of the mitral valve. The anterior descending branch of the left coronary artery showed marked sclerosis, with an eccentric lumen in the upper third; the distal two thirds of the lumen was completely obliterated. The posterior descending branch of the right

coronary artery was tortuous and sclerotic. The lumen was narrowed. The pericardial sac contained a small amount of clear fluid and was partly obliterated. The pericardium was adherent to the anterior lateral aspect of the left ventricle.

Microscopic study of a section of the myocardium in the region of the aneurysm (fig. 5) showed scar tissue with calcification and ossification, together with the formation of true marrow spaces in which all the cells usually found in bone marrow were represented.

The diagnosis was myocardial calcification with histologic evidence of bone formation.

Dr. Rosa Aronoff, pathologist, analyzed the pathologic material, and Dr. Leroy P. Van Winkle, roentgenologist, interpreted the roentgenograms.

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THERAPEUTIC VALUE OF CONVALESCENT SERUM IN SCARLET FEVER

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The Milwaukee Convalescent Serum Center, in the Columbia Hospital, since its establishment in February 1935 has made pooled human convalescent serum available for use in the prevention and treatment of various contagious diseases. The largest demand has been for serum from persons convalescent from scarlet fever, although there have been calls also for measles, mumps, acute poliomyelitis, chickenpox and normal serum.

The method of collecting, preparing and dispensing serum from patients convalescent from scarlet fever has been described,[1] and the methods of administration, the amounts recommended and the preliminary results have been discussed.[2] Further results obtained with the serum have been recorded through the use of follow-up cards sent to physicians who cared for the patients to whom the serum was given. The response to the questionnaire has been excellent. Only 29 of the 333 questionnaires sent out for information on the therapeutic results of scarlet fever serum remain unanswered. Another 10 were answered in an unsatisfactory manner.

This study is a comparison of the data for a total of 1,028 patients with scarlet fever, 139 of whom received the commercial antitoxin, 589 of whom received human convalescent serum and 300 of whom received neither antitoxin nor immune serum. All except 294 patients who received convalescent serum at home were treated in South View Hospital, the Milwaukee city isolation hospital.

The sex and average age incidence were approximately the same for all the groups. The majority (60.2 per cent) of patients treated at home had mild or moderately severe scarlet fever, whereas, among

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1. Hardgrove, M.: The Milwaukee Convalescent Serum Center, Minnesota Med. **18**:541-542 (Aug.) 1935.

2. Hardgrove, M.: The Use of Human Convalescent Serum in Infectious Diseases, Wisconsin M. J. **34**:812-816 (Nov.) 1935.

the patients in the hospital 100 per cent of those who received antitoxin and 95 per cent of those who received convalescent serum were severely ill or had complications. Neither of these serums was used in the routine treatment of patients with scarlet fever in the hospital.

Most (83 per cent) of the patients in the hospital were admitted before the fifth day of illness. The majority (79.3 per cent) of those who were cared for at home received convalescent serum within three days after the onset of the disease. The average length of time until a permanent normal temperature was reached after treatment was twelve and four-fifths days for the patients in the hospital who received antitoxin, four and one-half days for those in the hospital who received convalescent serum and only one and three-fifths days for those receiving convalescent serum at home. The patients in the control group reached a normal temperature on an average of ten and nine-tenths days after admission to the hospital. In this group were many patients with mild scarlet fever, which lowered the average length of time before a normal temperature was reached.

The average twelve hour fall in temperature for patients receiving convalescent serum was 3.5 F., as compared with 2.1 F. for those who were given antitoxin.

A satisfactory response was shown by 68.4 per cent of those treated at home who were given serum within a three day period and by 14.9 per cent of those who were given serum later than three days after the onset of the disease, making a total of 83.3 per cent. In 90 per cent of the hospital group a satisfactory response was observed after the use of convalescent serum, whereas only 60 per cent responded satisfactorily to antitoxin.

After the treatment was given complications persisted or new ones appeared in 35 per cent of those who received antitoxin treatment, 16 per cent of the hospital group and 12 per cent of those who received convalescent serum at home. These results compare favorably with those of Hoyne, Levinson and Thalhimer,[3] who showed that the incidence of complications was reduced approximately one-half through the early use of the serum.

The incidence of reactions after the use of convalescent serum was only 1 per cent, as opposed to 35 per cent after the use of commercial antitoxin. The early reactions noticed after the use of convalescent serum were transitory increases in temperature, chills and articular pains. Mild urticaria occasionally occurred within twenty-four hours

3. Hoyne, A. L.; Levinson, S. O., and Thalhimer, W.: Convalescent Scarlet Fever Serum: Its Prophylactic and Therapeutic Value; a Review of 2,875 Cases, J. A. M. A. **105**:783-789 (Sept. 7) 1935.

or two or three weeks later. The reactions did not seem to interfere with the beneficial effect of the serum, nor were they severe enough to cause serious concern. The reactions of immediate occurrence call attention to the fact that certain precautions should be taken when the serum is given. The serum should be warmed to body temperature in a water bath; overheating will coagulate the serum and make it unfit for use. The serum should be injected slowly, an all glass syringe that has been carefully cleaned and sterilized being used. More prompt results are obtained by intravenous therapy, but the precautions must be strictly observed.

The average dose given the patients treated at home was 33.6 cc. The individual doses ranged from 10 to 100 cc. The average dose of

Therapeutic Value of Convalescent Serum in Scarlet Fever

	Hospital Group			Home Group
	Control	Antitoxin	Convalescent Serum	Convalescent Serum
Number of patients (total, 1,028).....	300	139	295	294
Severe or complicated scarlet fever.....	57%	100%	93%	39.8%
Patients ill less than 5 days before hospitalization	83%	99%	87%	Less than 3 days, 79.3%
Average time until normal temperature was reached after admission to hospital	10.9 days	15.3 days	9.2 days	From onset of illness 4.25 days
Average time until normal temperature was reached after treatment	.....	12.8 days	4.58 days	1.66 days
Average 12 hour drop in temperature....	.....	2.1 F.	3.5 F.	3.4 F.
Satisfactory response	.....	60%	90%	First 3 days, 68.4%; after 3 days, 14.9%; total, 83.3%
Complications following treatment.....	.....	35%	10%	12.9%
Reactions	.....	33%	1%	1%
Deaths	6 (2%)	4 (2.8%)	8 (2.7%)	5 (1.7%)

convalescent serum given in the hospital was 32.7 cc., with a range of from 20 to 80 cc. per injection. In some cases these doses were repeated.

Park [4] found the mortality rate to be 2.8 per cent for 569 hospitalized patients with scarlet fever, 40 of whom received antitoxin. The groups discussed here are perhaps too small to warrant a comparison of the mortality rates, but it may be noted that the rate was much less for those treated at home (1.7 per cent). It must be remembered that only the very sick patients received convalescent serum or antitoxin in the hospital.

It is difficult to express statistically the satisfaction obtained in treating the scarlet fever patient with convalescent serum. In the

4. Park, W. H.: Scarlet Fever: Etiology, Prevention by Immunization, and Antitoxic Treatment, J. A. M. A. **85**:1180-1186 (Oct. 17) 1925.

majority of patients the results, as noted at the bedside, are striking. The higher the temperature and the more toxic the patient's condition, the better the results if the serum is given early. As a rule, after an intravenous injection has been given early to a patient with uncomplicated scarlet fever, his mind clears, the vomiting ceases, the appetite returns and the temperature and pulse rate begin to fall. Within from twelve to eighteen hours a patient who has been delirious and very sick will usually be convalescing. If the serum is given late in the disease or after complications have already set in, larger and repeated doses are often necessary.

The use of serum of patients convalescent from scarlet fever is to be encouraged in associated infections thought to be due to a (beta) hemolytic streptococcus.[5] Scarlet fever serum has been of value in the treatment of the erysipelas which appears as a result of contact with scarlet fever.[6] Improvement has also been noted as a result of its use in "surgical scarlet fever," following an operation or childbirth.

CONCLUSIONS

In a comparison of the results obtained in 139 patients with scarlet fever treated with commercial antitoxin, 589 treated with pooled human serum of patients convalescent from scarlet fever and 300 receiving neither but who received the same general symptomatic treatment, the most satisfactory results were observed after the use of convalescent serum.

When serum was given early in adequate doses, there was an apparent decrease in the mortality rate, as well as a reduction in the complications. As a rule, all the symptoms improved, and there was a marked reduction in the length of time until the temperature reached normal.

Serious untoward reactions following the use of human convalescent serum, given either intramuscularly or intravenously, have not been noted.

Excellent response has been obtained on the part of the physicians. It is through their cooperation that it is possible to estimate the value of this therapeutic agent among private patients treated at home.

5. Thalhimer, W., and Levinson, S. O.: Pooled Convalescent Scarlet Fever Treatment of Diverse Streptococcic Infections, J. A. M. A. **105**:864-866 (Sept. 14) 1935.

6. Fox, M. J.: The Biological Relationship Between Erysipelas and Scarlet Fever, Wisconsin M. J. **35**:797-801 (Oct.) 1936.

INCREASED URINARY EXCRETION OF IODINE IN HYPERTHYROIDISM

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Recently we [1] presented our findings concerning the normal urinary iodine of man, together with a review of the pertinent literature. At present few data [2] concerning the urinary loss of iodine in hyperthyroidism are available. These reveal a pathologic increase in the urinary excretion of iodine in certain patients with hyperthyroidism. We therefore became interested in making a more extensive investigation of this particular problem in order to determine significant variations from normal in the daily urinary loss of iodine of hyperthyroid patients.

Phillips and one of us (G. M. C.)[2a] observed in 1932 an increased urinary loss of iodine during certain phases of hyperthyroidism. Since that time others [3] have reported their investigations on patients with hyperthyroidism. The latter findings, on the whole, confirm the earlier ones.[2a, b] Our purpose in the present communication is to report an extensive investigation of the renal excretion of iodine of forty patients with hyperthyroidism studied over a total period of two hundred and ninety-eight days.

From the Department of Research Surgery, Ohio State University.

1. Curtis, G. M.; Puppel, I. D.; Cole, V. V., and Matthews, N. L.: The Normal Urinary Iodine of Man, J. Lab. & Clin. Med. **22**:1014, 1937.

2. (*a*) Curtis, G. M., and Phillips, F. J.: The Urinary Excretion of Iodine, J. Clin. Investigation **12**:963, 1933. (*b*) Scheffer, L.: Jodstoffwechsel bei Schilddrüsenkranken, Klin. Wchnschr. **12**:1285 (Aug. 19) 1933. (*c*) Curtis, G. M., and Phillips, F. J.: The Urinary Excretion of Iodine in Toxic Goiter, J. A. M. A. **101**:1992 (Dec. 16) 1933. (*d*) Szász, E.: Ueber Jodausscheidung gesunder und hyperthyreoter Menschen im Höhenklima, Med. Klin. **29**:1584 (Nov. 17) 1933. (*e*) Elmer, A., and Scheps, M.: The Iodine Content of Blood and of Urine and the Basal Metabolic Rate: Their Value in the Diagnosis of the Function of the Thyroid Gland, Acta med. Scandinav. **82**:126, 1934. (*f*) Scheffer, L.: Ueber die Rolle des Jods bei der Entstehung von Schilddrüsenkrankheiten, Schweiz. med. Wchnschr. **64**:969 (Oct. 20) 1934; (*g*) Jodstoffwechsel bei Hyperthyreosen, Klin. Wchnschr. **13**:1570 (Nov. 3) 1934. (*h*) Scheffer, L., and von Megay, L.: Jodstoffwechsel bei Kropfträgern, ibid. **14**:1360 (Sept. 21) 1935. (*i*) Elmer, A., and Scheps, M.: La thyroxine est-elle éliminée par les reins chez l'homme normal et chez les basodowiens? Compt. rend. Soc. de biol. **115**:968, 1934.

3. Scheffer.[2b] Szász.[2d] Elmer and Scheps.[2e] Scheffer.[2f, g] Scheffer and von Megay.[2h] Elmer and Scheps.[2i]

METHODS

The ward and laboratory methods were essentially similar to those presented in a previous report.[1] The patients were all investigated preoperatively. They did not receive thyroid therapy or any form of iodine medication for at least two weeks previous to or during this study. The daily diets were of high caloric value. Foods of known high iodine content,[4] particularly sea foods, were excluded. The early analyses of the iodine of the blood and urine were all made by the method of Phillips and one of us (G. M. C.).[5] Others were made by the Matthews [6] modification of the Leipert [7] procedure.

OBSERVATIONS

The forty patients all presented the characteristic clinical picture of hyperthyroidism, and the diagnosis was confirmed after extensive observation and investigation. Their ages varied from 14 to 57 years. Thirty-three were females, and seven were males. They presented no other recognized abnormality, such as evidence of renal damage, which might so far as is known affect iodine metabolism. The forty patients were divided into three groups, those with exophthalmic goiter, toxic nodular goiter and unusual forms of hyperthyroidism.

EXOPHTHALMIC GOITER

The daily urinary excretion of iodine was determined over a total period of one hundred and ninety-nine days for twenty-four patients (table 1) with exophthalmic goiter. Their ages varied from 14 to 48 years. Eighteen were females and six were males. These patients excreted daily from 29 to 730 micrograms of iodine in the urine, with averages ranging from 46 to 357 micrograms. The grand average was 147 micrograms per twenty-four hours. The average concentration of iodine in the urine was 12.3 micrograms per hundred cubic centimeters.

The grand average basal metabolic rate was plus 54 per cent. The rate was elevated in twenty-three patients and normal in one patient (table 1, patient 18). The average iodine content of the blood was greatly increased in twenty-one patients, slightly increased in one patient (table 1, patient 3) and normal in two patients (table 1, patients 6 and 15). The average daily urinary loss of iodine was increased in eighteen and normal in six patients (table 1, patients 3, 4, 7, 13, 19 and 22).

4. Cole, V. V.; Curtis, G. M., and Bone, M. L.: The Iodine Content of Hospital Foods, J. Am. Dietet. A. **10**:200, 1934.

5. Phillips, F. J., and Curtis, G. M.: The Clinical Determination of Iodine in Blood, Urine, and Feces, Am. J. Clin. Path. **4**:346, 1934.

6. Matthews, N. L.: To be published.

7. Leipert, T.: Die Bestimmung kleinster Jodmengen in organischem Material, Biochem. Ztschr. **261**:436, 1933; Zur Kenntnis des physiologischen Blutjodspiegels, ibid. **270**:448, 1934.

One (approximately 4 per cent) of the twenty-four patients with exophthalmic goiter presented a normal basal metabolic rate (table 1, patient 18). However, there was a greatly increased urinary excretion of iodine. Two patients (approximately 8 per cent) showed a normal average content of blood iodine (table 1, patients 6 and 15). These revealed an elevated average basal metabolic rate and an increased urinary excretion of iodine. The six patients with a normal urinary

TABLE 1.—*Urinary Loss of Iodine in Exophthalmic Goiter*

Date	Patient Number	Patient	Sex	Age	Basal Metabolic Rate, % Plus	Days of Investigation	Average 24 Hour Urinary Volume, Cc.	Average Urinary Concentration of Iodine, Micrograms per 100 Cc.	Limits of Daily Urinary Excretion of Iodine, Micrograms		Average 24 Hour Urinary Excretion of Iodine, Micrograms
									Low	High	
Dec. 1932	1	M. F.	F	35	42	2	950	19.9	108	214	161
Jan. 1933	2	J. B.	F	32	19	5	1,115	14.9	55	165	106
March 1933	3	F. M.	F	18	37	13	2,635	2.6	34	122	64
April 1933	4	C. W.	M	38	54	20	950	9.5	29	186	69
May-June '33	5	H. C.	F	17	18	8	805	28.9	87	257	173
June 1933	6	H. L.	F	37	91	7	1,125	10.0	36	233	117
July 1933	7	G. M.	F	25	88	1	570	8.1	...	...	46
Aug. 1933	8	D. S.	F	51	109	4	1,370	14.9	133	253	206
Oct. 1933	9	M. W.	F	25	64	4	1,060	14.5	92	225	176
Oct. 1933	10	J. P.	M	48	84	4	1,945	12.6	74	395	251
Oct. 1933	11	F. P.	M	39	47	4	1,885	7.7	83	213	134
Nov. 1933	12	R. D.	F	37	75	4	1,045	21.5	101	401	241
April 1934	13	T. F.	F	24	28	15	.....	....	44	63	52
Nov. 1934	14	R. S.	F	24	79	14	1,235	12.1	68	256	131
Feb. 1935	15	E. T.	F	21	52	1	780	22.7	...	...	178
June 1935	16	R. B.	F	22	36	10	1,200	7.1	55	110	82
Oct.-Nov. '35	17	S. T.	F	57	23	15	2,190	9.8	36	269	100
Oct.-Nov. '35	18	C. C.	M	44	11	3	2,175	7.5	219	297	245
Dec. 1935	19	V. M.	F	44	38	7	1,495	3.9	29	102	59
Mar.-Apr. '36	20	O. C.	M	35	61	10	1,575	13.2	110	258	194
April 1936	21	M. W.	F	14	29	3	1,490	14.2	186	246	209
June 1936	22	L. W.	F	19	49	19	1,350	4.5	35	97	60
July-Aug. '36	23	L. A.	F	22	62	7	1,730	8.0	71	181	123
July-Aug. '36	24	F. W.	M	23	92	19	2,475	15.7	148	730	357
Grand averages					54	8.3	1,440	12.3			147
Low and high limits of daily urinary excretion of iodine									29	— 730	46—357

iodine content showed an elevated average basal metabolic rate and an increased average blood iodine content. Gross and microscopic examination of the goitrous tissue removed at operation confirmed the diagnosis of exophthalmic goiter in each case.

The highest urinary excretion of iodine (730 micrograms) for this series of patients with exophthalmic goiter occurred in a patient (table 1, patient 24) presenting a greatly increased energy metabolism and the exaggerated clinical features characteristic of an impending crisis of hyperthyroidism. Subsequent partial amelioration of the symptoms was accompanied by a lowering (to 148 micrograms per day) of the increased urinary iodine.

TOXIC NODULAR GOITER

There were nine patients (eight women and one man) with toxic nodular goiter. These (table 2) were investigated over a total period of forty-eight days. The ages varied from 22 to 56 years. These patients excreted daily from 31 to 954 micrograms of iodine in the urine, with averages of from 39 to 593 micrograms. The grand average was 214 micrograms per twenty-four hours. The grand average concentration of iodine in the urine was 20 micrograms per hundred cubic centimeters.

The grand average basal metabolic rate was plus 21 per cent. It was elevated in eight patients and normal in one patient (table 2, patient 6). The average value for blood iodine was increased in eight patients and normal in one patient (table 2, patient 2). The average

TABLE 2.—*Urinary Loss of Iodine in Toxic Nodular Goiter*

Date	Patient Number	Patient	Sex	Age	Basal Metabolic Rate, % Plus	Days of Investigation	Average 24 Hour Urinary Volume, Cc.	Average Urinary Concentration of Iodine, Micrograms per 100 Cc.	Limits of Daily Urinary Excretion of Iodine, Micrograms		Average 24 Hour Urinary Excretion of Iodine, Micrograms
									Low	High	
Jan. 1933	1	B. N.	F	22	16	5	945	6.2	51	73	64
Feb. 1933	2	D. R.	F	27	18	3	425	46.7	85	276	201
Feb. 1933	3	C. C.	F	31	19	8	1,780	15.1	196	314	269
Aug. 1933	4	L. M.	F	24	18	3	1,235	31.5	282	448	377
July 1935	5	P. B.	F	44	42	10	1,360	47.1	181	954	593
Nov. 1935	6	C. H.	F	54	0	5	835	11.5	69	111	90
Dec. 1935	7	E. S.	M	52	22	10	1,405	2.8	31	64	39
Jan. 1936	8	M. H.	F	36	24	1	1,690	9.5	...	...	161
Jan. 1937	9	S. W.	F	53	21	3	1,265	10.4	...	...	132
Grand average					20	5.3	1,215	20.1			214
Low and high limits of daily urinary excretion of iodine									31	— 954	39—593

daily urinary excretion of iodine was greatly increased in six patients, slightly increased in one patient (table 2, patient 6) and normal in two patients (table 2, patients 1 and 7).

One patient (approximately 11 per cent) showed a normal basal metabolic rate (table 2, patient 6). However, there was an increased content of iodine in the blood and urine. Another (approximately 11 per cent) showed a normal value for blood iodine (table 2, patient 2). The basal metabolic rate was only slightly elevated; however, the urinary excretion of iodine was greatly increased. Two patients (approximately 22 per cent) disclosed a normal average urinary excretion of iodine (table 2, patients 1 and 7). The basal metabolic rate was slightly increased in one patient (table 2, patient 1) and plus 22 per cent in the other (table 2, patient 7). The value for blood iodine was increased in both.

UNUSUAL FORMS OF HYPERTHYROIDISM

Two patients with mixed goiter (table 3) showed an elevated basal metabolic rate, an increased blood iodine content and an increased urinary excretion of iodine. A patient with carcinoma of the thyroid gland (table 3) revealed an elevated basal metabolic rate, a normal value for blood iodine and an increased urinary excretion of iodine. A patient with induced hyperthyroidism, investigated immediately after the cessation of excessive thyroid medication (table 3), revealed an elevated basal metabolic rate, a definitely increased blood iodine content and a greatly increased urinary excretion of iodine. Of the three patients having pseudorecurrent hyperthyroidism (table 3), patients E. R. and M. R. revealed an elevated basal metabolic rate and patient D. B. a normal

TABLE 3.—*Urinary Loss of Iodine in Unusual Forms of Hyperthyroidism*

Type	Patient	Sex	Age	Basal Metabolic Rate, % Plus	Days of Investigation	Average 24 Hour Urinary Volume, Cc.	Average Urinary Concentration of Iodine, Micrograms per 100 Cc.	Limits of Daily Urinary Excretion of Iodine, Micrograms		Average 24 Hour Urinary Excretion of Iodine, Micrograms
								Low	High	
Mixed goiter.....	M. H.	F	38	49	7	1,235	40.8	405	628	483
Mixed goiter.....	M. K.	F	37	61	2	1,175	24.3	157	428	293
Carcinoma.....	F. B.	F	52	35	13	3,540	10.2	103	832	362
Induced hyperthyroidism	E. H.	F	17	16	3	1,635	41.2	302	600	467
Pseudorecurrent hyperthyroidism*	E. R.	F	44	34	6	3,190	2.2	53	98	70
	M. R.	F	25	50	13	1,000	19.6	84	276	189
	D. B.	F	28	13	7	600	5.2	13	60	30

* Pseudorecurrent hyperthyroidism refers to recurrent hyperthyroidism following insufficient surgical removal of goitrous tissue or subsequent to removal of a single lobe.

rate. The blood iodine content was increased in patients M. R. and D. B. and normal in patient E. R. The daily urinary excretion of iodine was increased in patient M. R. but normal in patients E. R. and D. B.

COMMENT

Iodine is a normal constituent of human urine.[1] The daily physiologic fluctuation [1] in its excretion by the kidney may be great (chart). Two hundred and twenty-seven daily determinations of the urinary iodine content made for thirteen persons without evidence of thyroid disease gave a range of from 7 to 196 micrograms per twenty-four hour period, with averages of from 36 to 78 micrograms.[1] The grand average was 51 micrograms per twenty-four hour period. This daily fluctuation may be due to many normal variables which affect iodine metabolism, such as the qualitative and quantitative intake of iodine, the geographic region, the activity of the thyroid gland, the metabolism of the

thyroid hormone in the extrathyroid tissues, emotion and the excretion of iodine through other channels, such as the skin and the gastrointestinal tract. Nevertheless, normal persons maintained for days on a constant regimen [8] (chart) show only a small range in the daily urinary output of iodine.

Pathologically, the greatest increase in the urinary excretion of iodine occurs in certain patients with hyperthyroidism, as revealed in tables 1 to 4. The grand average value for urinary iodine for these forty patients was 184 micrograms per day, which is between three and four

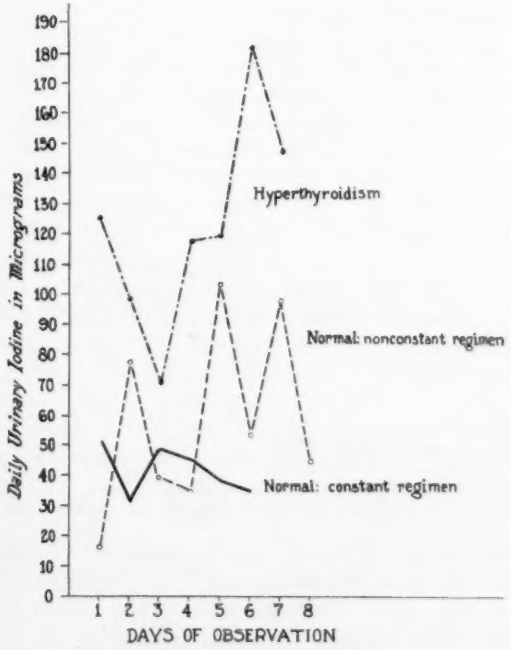

Chart showing a comparison of the urinary excretion of iodine in a patient with hyperthyroidism (L. A., table 1, patient 23), in a normal patient [1] (patient C. S.) on a nonconstant regimen and in a normal patient [8b] (patient R. B.) on a constant regimen.

times greater than the normal grand average [1] for persons in the same region. This increase in the urinary excretion of iodine in patients with hyperthyroidism was not necessarily accompanied with an increased

8. Puppel, I. D., and Curtis, G. M.: (*a*) Calcium and Iodine Metabolism in Thyroid Disease, Arch. Int. Med. **58**:957 (Dec.) 1936; (*b*) Unpublished data.

urinary volume. In the majority of patients it was accompanied with a greater urinary concentration of iodine (tables 1 to 4) than normal.[1]

The grand average daily urinary loss of iodine in toxic nodular goiter was greater than that in exophthalmic goiter. The cause for this remains obscure.

Data (table 3) concerning the urinary excretion of iodine in mixed goiter and carcinoma of the thyroid gland with hyperthyroidism, in induced hyperthyroidism and in pseudorecurrent hyperthyroidism are presented. These findings are in harmony with those for exophthalmic goiter and toxic nodular goiter; however, there are too few cases from which to draw extensive conclusions.

These data (tables 1 to 4 and chart) show that the variability of the daily urinary excretion of iodine in hyperthyroidism was much

TABLE 4.—*Summary of the Urinary Loss of Iodine in Various Types of Hyperthyroidism*

Type of Goiter	Number of Patients	Total Days of Investigation	Average 24 Hour Urinary Volume, Cc.	Average Urinary Concentration of Iodine, Micrograms per 100 Cc.	Limits of Daily Urinary Excretion of Iodine, Micrograms		Average 24 Hour Urinary Excretion of Iodine, Micrograms
					Low	High	
1. Exophthalmic	24	199	1,440	12.3	29	730	147
2. Nodular	9	48	1,215	20.1	31	954	214
3. Unusual forms							
Mixed	2	9	1,205	32.6	157	628	388
Carcinoma	1	13	3,540	10.2	103	832	362
Induced hyperthyroidism	1	3	1,635	41.2	302	600	467
Pseudorecurrent hyperthyroidism*	3	26	1,595	9.0	13	276	96

* Pseudorecurrent hyperthyroidism refers to recurrent hyperthyroidism following insufficient surgical removal of goitrous tissue or subsequent to removal of a single lobe.

greater than normal.[1] It ranged from 13 to 954 micrograms daily, with averages of from 30 to 593 micrograms. One hundred and ten (37 per cent) of the two hundred and ninety-eight daily determinations of the urinary iodine were normal. There was great variation (tables 1 to 4) in daily urinary excretion of iodine not only for different patients with hyperthyroidism but for the same patient. The variations ranged from the finding of all normal values for one patient (table 1, patient 13) over a period of fifteen days to the finding of all increased values in another patient (table 1, patient 24) over a period of nineteen days. Certain patients showed fluctuations from low normal to greatly increased values during successive days. These variations in the urinary excretion of iodine for the same patient and for different patients with hyperthyroidism correspond to the variations which may occur in any one of the other clinical and laboratory features of this disease.

The basal metabolic rate (tables 1 to 3) was variable. The urinary iodine content did not necessarily vary with the basal metabolic rate or with the value for blood iodine, either in the same patient or in different patients with hyperthyroidism. In 7.5 per cent of the forty patients the basal metabolic rate remained within the normal range. However, there was an increased blood iodine content or an increased urinary excretion of iodine or both. Twelve and one-half per cent of the forty patients showed a normal blood iodine value, but the basal metabolic rate or the urinary excretion of iodine or both were increased. In 25 per cent of the patients the average daily urinary excretion of iodine remained within normal limits. These patients showed an elevated basal metabolic rate or an increased blood iodine value or both. Gross and microscopic examination of the surgically removed goitrous tissue of the twenty-four patients with exophthalmic goiter confirmed the preoperative diagnosis of exophthalmic goiter.

Increased urinary excretion of iodine is also sometimes observed in conditions other than clinical hyperthyroidism. It may be noted in lymphatic and myelogenous leukemias;[9] in essential hypertension, hypertensive heart disease or in certain cases in congestive heart failure;[9] during certain phases of the menstrual cycle[10] or certain stages of pregnancy;[11] transiently subsequent to thyroid[12] or extrathyroid operations,[13] and during or immediately after the administration of thyroid or iodine medication[1] in any form. These conditions may be diagnostically eliminated by adequate clinical and laboratory examination of the patient.

Determinations of the blood and urinary iodine are at present of the greatest importance in recognizing cases of borderline or incipient hyperthyroidism in which there is a normal basal metabolic rate but an increased rate of iodine metabolism. They are of differential diagnostic importance in cases of neurocirculatory asthenia in which the clinical features simulate borderline hyperthyroidism but in which there is a normal iodine metabolism.[8b]

In exophthalmic goiter there occurs an increased mobilization and elimination of the body iodine, so that the patient may be in negative

9. Curtis, G. M., and Barron, L. E.: The Urinary Loss of Iodine Following Total Thyroidectomy, Surgery **1**:92, 1937.

10. Cole, V. V., and Curtis, G. M.: Cyclic Variations in Urinary Excretion of Iodine in Women, Proc. Soc. Exper. Biol. & Med. **31**:29, 1933.

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iodine balance [14] during certain stages of the disease even in the presence of a normally adequate intake of iodine. At present it is not certain that the incipient thyroid hyperplasia precedes or follows the onset of this process of increased utilization, mobilization and excretion of iodine. However, it is possible that the thyroid hyperplasia in hyperthyroidism is secondary to the increased loss of body iodine and is compensatory in an attempt to meet a continued bodily demand for utilizable iodine after the store of utilizable iodine has been depleted.

Increased urinary excretion of iodine by patients with hyperthyroidism (table 4) is an indication of this state of increased loss of body iodine. However, there may be an increased excretion of iodine through other channels, such as the gastro-intestinal tract [15] and the skin,[2b] with a normal renal excretion of iodine.

The percentage of increase in the fecal excretion of iodine in hyperthyroidism is often greater [14a] than that of the increased urinary excretion of iodine. Consequently, a normal urinary excretion of iodine in hyperthyroidism does not necessarily indicate that there is not a pathologically increased loss of iodine from the body. A normal urinary excretion of iodine in hyperthyroidism may be accompanied with an increased output of iodine through other channels [16] or may be a result of renal insufficiency with retention of iodine [17] or possibly a result of depletion of stored utilizable iodine.

As evidence of at least partial depletion of the depots of utilizable iodine of the body in hyperthyroidism is the decreased iodine content of the thyroid [18] in noniodized patients. Another point of evidence is the increased excretion of iodine over normal with a similar intake of iodine.[19] A third point of evidence of a state of partial depletion in certain patients with hyperthyroidism is increased retention of iodine [8b] which occurs immediately subsequent to the administration of iodine, for instance, in iodized milk or potassium iodide. The latter evidence is also revealed in the resulting iodine-induced colloid involution, with an

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19. Cole and Curtis.[14a] Scheffer.[2b]

increased content of iodine in the thyroid gland in exophthalmic goiter,[18c] and by the accompanying smaller excretion of iodine as compared with the normal.[8b]

If the negative iodine balance of hyperthyroidism continues over a sufficient time, it is readily appreciated that a state of depletion of the available stores of iodine in the body may occur. The intensity of the hyperthyroidism should then change unless a sufficient amount of iodine is supplied to maintain the increased blood iodine content and the increased loss of body iodine. This state of depletion of the store of utilizable iodine of the body in the absence of a sufficient intake of iodine may actually occur and may explain at least some of the remissions of exophthalmic goiter. Further investigation of these particular problems concerning the nature of the urinary iodine and the iodine balance in hyperthyroidism should prove of the greatest importance.

SUMMARY

There is an increased urinary excretion of iodine in certain cases and phases of hyperthyroidism. The grand average value for urinary iodine in forty patients investigated over a period of two hundred and ninety-eight days was 184 micrograms per day, which is between three and four times greater than the normal grand average (51 micrograms) for persons living in central Ohio.

The grand average daily urinary excretion of iodine in toxic nodular goiter was greater than that in exophthalmic goiter. The cause for this is not clear.

The variability of the daily urinary excretion of iodine in hyperthyroidism is much greater than that of the normal urinary excretion of iodine. It ranged from 13 to 954 micrograms daily, with averages ranging from 30 to 593 micrograms. The many variations in the urinary excretion of iodine in the same patient and in different patients with hyperthyroidism correspond to the many variations which may occur in any of the other clinical and laboratory features of this disease.

An increased urinary excretion of iodine is sometimes observed also in conditions other than clinical hyperthyroidism.

Determinations of the blood and urinary iodine are at present of the greatest differential diagnostic importance in certain cases of neurocirculatory asthenia in which the clinical features simulate borderline hyperthyroidism.

Increased urinary excretion of iodine by patients with hyperthyroidism is an indication of a state of increased loss of body iodine. However, a normal urinary excretion of iodine in hyperthyroidism does not necessarily indicate that there is not a pathologic increased loss of the body iodine. A normal urinary excretion of iodine in hyperthyroidism may

be accompanied with an increased output of iodine through other channels, or it may be a result of renal insufficiency with retention of iodine, or, possibly, a result of depletion of available utilizable iodine.

Evidences of at least partial depletion of the stores of utilizable iodine in patients with hyperthyroidism are present in the decreased iodine content of the thyroid gland, the negative iodine balance even with a normally adequate intake of iodine and the increased retention of iodine which occurs immediately subsequent to the administration of iodine in any form.

At present it is not certain whether the incipient thyroid hyperplasia precedes or follows the onset of this process of increased mobilization, utilization and excretion of iodine. However, it is possible that the thyroid hyperplasia in hyperthyroidism is secondary to the increased loss of body iodine and that it is compensatory in an attempt to meet a continued increased demand for utilizable iodine after the store of utilizable iodine has been consumed.

A state of depletion of the store of ultilizable iodine of the body in the absence of a sufficient intake of iodine may actually occur and explain at least certain of the spontaneous remissions of exophthalmic goiter. Further investigation of these particular problems concerning the nature of the urinary iodine and the iodine balance in hyperthyroidism should prove of the greatest importance.

The National Research Council furnished the grant which made possible the completion of these studies. Dr. Francis J. Phillips and Dr. Versa V. Cole rendered invaluable aid during the early work. The determinations of the basal metabolic rate and the iodine analyses were made with the assistance of Norman L. Matthews, J. H. Meyer and Ruth Bierbaum.

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ELECTROLYTES OF BLOOD AND URINE OF DOGS WITH ACUTE HEPATIC INJURY PRODUCED BY ARSPHENAMINE

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Investigations of the effects of experimental hepatic injury on the chemical constituents of the blood have been of limited character. Most of the investigations have been concerned with changes in the nonprotein nitrogen, urea and uric acid of the blood and alterations in carbohydrate metabolism. Minot and Cutler [1] have described increases in the guanidine base and accumulations of lactic acid in the blood in instances of damage to the parenchyma of the liver produced experimentally by carbon tetrachloride poisoning. Occasional clinical reports [2] have described the reduction of plasma chlorides in instances of carbon tetrachloride intoxication, while an increase in the concentration of lactic acid in the blood of patients with extensive hepatic disease has been described by several authors.[3]

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From the Medical Service of Dr. George Baehr and the Laboratories of the Mount Sinai Hospital.

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In a previous paper one of us (L. J. S.[4]) reported the existence of changes in the electrolytes of the blood following the production of extensive hepatic damage with arsphenamine.

In the present study these changes were further investigated. Determinations were made of the nonprotein nitrogen, urea, sugar, carbon dioxide, sodium, chloride, potassium, calcium, phosphorus, magnesium, total protein and lactic acid contents of the blood, as well as complete hematologic studies in several instances. In two dogs careful studies of the urine were conducted which included quantitative determinations of the total protein, chloride, inorganic phosphate and lactic acid contents.

PROCEDURE

Hepatic damage was produced in dogs by intravenous injection of arsphenamine. The animals were kept on a diet of raw shin meat to which 2 Gm. of salt was added daily for at least two weeks before the experiment was started. Just before the injection of arsphenamine, blood from the femoral artery was collected anaerobically for the determination of the various electrolytes.

All determinations on the blood were made with serum. Sodium was studied by the method of Butler and Tuthill;[5] potassium, by the colorimetric method of Shohl and Bennett;[6] calcium and magnesium, by the method of Kramer and Tisdall;[7] carbon dioxide, by that of Van Slyke and Neill;[8] inorganic phosphate, by that of Fiske and Subbarrow;[9] chloride, by that of Van Slyke;[10] lactic acid, by that of Friedemann and his associates;[11] urea, by decomposition with urease and direct nesslerization, ghatti gum being used as a stabilizing colloid (Folin[12]), and nonprotein nitrogen, by direct nesslerization (Wong[13]). The total protein content was determined by the refractometric method.

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The methods employed for the determination of the various urinary constituents were as follows: Total protein was determined by the colorimetric method of Wu and Ling;[14] chloride, by the modified Volhard-Harvey titration method;[15] lactic acid, by that of Friedemann and his associates,[11] and inorganic phosphate, by that of Fiske and Subbarow.[9]

From 40 to 80 mg. per kilogram of body weight of freshly prepared arsphenamine was injected intravenously. This was usually followed in about one-half hour by vomiting, which lasted a few minutes and then subsided entirely. Five of eleven animals required subsequent injections of arsphenamine for the production of icterus. Death usually occurred from twenty to twenty-four hours after the last injection of arsphenamine. Samples of arterial blood were again collected for study of the electrolytes when the animal appeared definitely icteric. From six to eight hours after the appearance of jaundice the dogs became comatose and died. At no time were convulsive seizures manifested. In three instances (dogs 12, 21 and 24) there was no visible jaundice. The bilirubin content of the blood, however, was somewhat elevated, and bile was excreted in the urine. At autopsy the liver showed extensive destruction in all three instances, although the destruction was not as pronounced as in the severely jaundiced animals.

Immediately after the death of each animal autopsy was performed, and sections of the liver, kidneys and intestines were removed for microscopic study. Two of the eleven dogs presented considerable congestion of the small intestine and rectum. The kidneys appeared grossly normal in all instances. The liver felt firm but had a distinctly mottled appearance. The lobules were well outlined and were surrounded by punctate hemorrhages. The remaining organs appeared entirely normal. Microscopically the liver showed the most pronounced changes. In dog 1 there was extensive central necrosis, well over three fourths of the individual lobules being destroyed. There were some well preserved cells around the periportal spaces, but even here some necrosis was present. In many areas the necrosis extended to the portal vein. The cellular structure of the lobule was entirely destroyed. The kidneys of this animal showed much less marked changes. Many of the glomerular capsules showed the presence of a coagulated fluid. There was no actual damage, however, to the glomeruli. There was occasional necrosis of some of the cells of the tubular epithelium. The nuclei of many had disappeared. The tubular epithelium in places was swollen, granular and vacuolated. The remaining dogs showed similar microscopic changes but to varying degrees. In all instances the most pronounced changes occurred in the parenchymal cells of the liver.

RESULTS

Of the eleven dogs thus studied, nine died and two survived. Jaundice developed in the animals that survived, and the animals appeared to be as ill clinically as were those that failed to recover. However, the electrolyte pattern of the blood of these animals at the height of the illness differed from that of the other experimental animals. The details of these experiments will be described subsequently.

In eight of the eleven dogs icterus developed. The bilirubin content of the blood varied from 2 to 16 mg. per hundred cubic centimeters,

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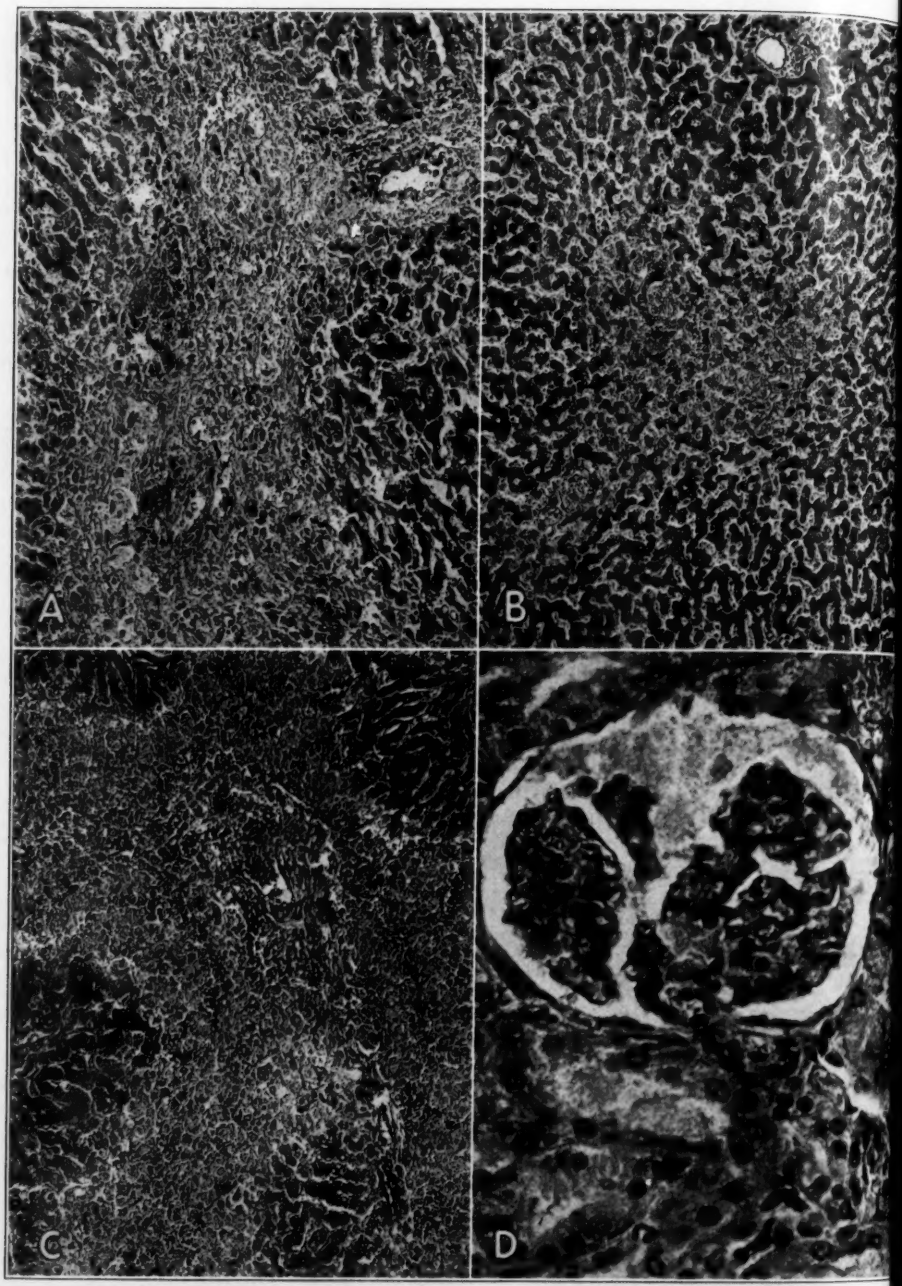

Fig. 1.—*A*, a section from the liver of dog 8, showing severe central destruction of the parenchyma; medium power. *B*, a section from the liver of dog 12, showing mild central parenchymal destruction and congestion; medium power. *C*, a section from the liver of dog 14, showing severe central parenchymal necrosis; medium power. *D*, a section from the kidney of dog 1; high power. Note the tubular degeneration and exudate in Bowman's capsule.

TABLE 1.—*Protocols of Experiments*

Dog No.	Van den Bergh Test		Icterus Index, Units	Volume of Packed Erythrocytes, Cc. per 100 Cc.	Volume of Packed Leukocytes, Cc. per 100 Cc.	Plasma Volume, Cc. per 100 Cc.	Date	Time	Arsphenamine, Mg. per Kg. of Body Weight	Intravenous Injection, Cc.	Comment
	Qualitative	Quantitative									
1	Negative	0.5	6	48.5	1.0	50.5	11/26	2:30 p.m.	60	76.0	Control
	Delayed; biphasic	2.5	20	65.0	0.5	34.5	11/27	12:10 p.m.	..	....	Dog died
4	Negative	0.5	6	42.0	1.5	56.5	12/ 7	10:30 a.m.	53	78.0	Control
	Negative	...	..	....	...	....	12/13	2:45 p.m.	60	88.0	
							12/18	8:00 p.m.	70	101.5	
	Delayed; biphasic	3.6	56	51.0	0.9	48.1	12/20	8:00 a.m.	..	....	Dog died
8	Negative	0.5	6	....	...	....	7/ 8/35	10:00 a.m.	60	56.0	Control
							7/10	10:00 a.m.	70	66.0	
	Direct	10.0	100+	....	...	....	7/11	3:30 p.m.	80	75.0	
							7/12	8:00 p.m.	..	....	Dog died
10	Negative	0.5	4	33.3	1.5	65.2	7/19/35	10:00 a.m.	50	61.0	Control
							7/20/35	10:30 a.m.	50	61.0	
	Prompt; biphasic	3.7	100	42.1	1.5	56.4	7/22/35	4:00 p.m.	..	....	Dog died
12	Negative	0.5	6	33.1	0.8	66.1	7/24/35	10:00 a.m.	40	38.0	Control
							7/25/35	10:00 a.m.	50	47.0	
	Very faint; delayed; biphasic	0.5	7	41.6	2.0	56.4	7/26/35	8:30 a.m.	..	....	Dog died
14	Negative	0.5	5	36.4	1.5	62.1	7/29/35	10:00 a.m.	40	45.0	Control
	Direct	5.7	60	41.0	1.8	57.2	7/30/35	11:00 a.m.			
							7/31/35	10:15 a.m.			
	Direct	16.0	100	46.2	1.4	52.4	7/31/35	11:15 a.m.	..	....	Dog died
19	Negative	0.5	5	33.6	0.9	65.5	6/ 3/36	10:00 a.m.	60	54.0	Control
							6/ 8/36	10:00 a.m.	80	69.0	
	Direct	2.5	30	38.1	0.6	61.3	6/ 9/36	11:00 a.m.			
	Direct	5.6	90	40.0	0.6	59.4	6/10/36	9:30 a.m.	..	....	Dog died
21	Negative	0.5	..	38.5	1.5	60.0	9/29/36	11:30 a.m.	65	65.0	Control
	Indirect	1.0	..	....	...	....	10/31/36	2:30 p.m.	..	....	Dog died
24	Negative	0.5	..	32.5	2.0	65.5	10/21/36	12:00 m.	70	56.0	Control
	Indirect	0.8	..	....	...	....	10/23/36	10:00 a.m.	..	....	Dog died
3	Negative	0.5	..	40.0	1.5	58.5	12/ 7/34	10:30 a.m.	55	75.0	Control
	Delayed; biphasic	2.0	..	48.5	2.0	49.5	12/ 8/34	2:30 p.m.	..	....	Dog recovered
18	Negative	0.5	4	42.8	1.0	56.2	5/20/36	1:30 p.m.	85	85.0	Control
	Direct	4.4	50	41.5	1.0	57.5	5/21/36	4:30 p.m.	..	....	Dog recovered

TABLE 2.—*Serum Electrolytes in Acute Hepatic Parenchymal Damage*

Dog No.	Nonprotein Nitrogen, Mg. per 100 Cc.	Urea, Mg. per 100 Cc.	Sugar, Mg. per 100 Cc.	Carbon Dioxide Content, Milli-equivalents per Liter	Sodium, Milli-equivalents per Liter	Chloride, Milli-equivalents per Liter	Potassium, Milli-equivalents per Liter	Calcium, Mg. per 100 Cc.	Inorganic Phosphorus, Mg. per 100 Cc.	Magnesium, Mg. per 100 Cc.	Lactic Acid, Mg. per 100 Cc.	Total Protein, Gm. per 100 Cc.	Date
1	26	11	80	24.4	144.6	114.4	4.0	9.6	3.4	...	16.4	5.6	11/26
	84	53	16	12.5	145.8	107.0	13.5	9.5	12.9	...	85.0	5.4	11/27
4	36	18	85	29.5	145.3	107.5	4.1	11.8	6.6	1.6	19.5	5.5	12/ 7
	35		85										
	88	41	20	19.7	138.0	100.4	11.3	11.6	18.0	4.3	80.0	5.1	12/20
8	31	..	83	26.4	147.0	110.6	....	10.4	3.5	...	13.4	4.9	7/ 8/35
	108	..	100	19.5	146.9	93.6	....	....	6.6	...	35.8	5.2	7/11
10	30	17	70	26.7	143.3	111.4	4.9	10.0	4.4	1.8	11.7	4.8	7/19/35
	76	56	32	17.2	138.4	101.6	5.6	9.5	15.4	2.4	47.0	4.8	7/22/35
12	30	12	88	22.4	140.3	109.0	4.1	10.2	4.0	1.2	13.4	7.0	7/24/35
	128	100	92	14.6	138.2	94.8	5.7	9.3	16.0	2.4	24.6	6.5	7/26/35
14	34	18	72	27.6	143.0	104.0	5.9	10.2	3.3	...	10.4	6.1	7/29/35
	40	25	90	23.4	139.0	99.4	...	9.8	3.8	...	29.1	5.6	7/30/35
			60								40.2		
	90	75	50	21.4	137.1	85.8	7.6	10.4	11.4	...	70.0	6.1	7/31/35
19	30	15	85	26.8	147.5	104.0	5.5	10.5	3.8	2.3	12.9	6.7	6/ 3/36
	56	30	90	19.0	133.9	95.0	5.6	9.9	3.8	2.0	30.7	6.2	6/ 9/36
	128	88	75	16.2	134.0	86.0	8.3	9.7	6.9	2.8	74.3	6.2	6/10/36
21	35	15	95	26.0	140.0	108.0	...	11.8	4.0	...	16.0	6.7	9/29/36
	70	52	85	19.6	137.2	95.0	...	10.9	8.2	...	36.5	6.9	10/31/36
24	28	15	70	24.7	140.0	105.4	...	11.2	5.3	...	10.5	5.6	10/21/36
	60	40	80	19.0	136.0	96.5	...	11.0	8.5	...	32.0	6.0	10/23/36
3	36	15	70	27.0	145.6	109.6	3.8	11.3	6.6	1.5	18.9	5.0	12/ 7/34
	50	22	75	27.4	140.3	99.0	4.4	10.9	6.9	1.5	18.9	5.0	12/ 8/34
18	40	19	100	19.2	142.5	103.0	7.9	10.9	3.2	...	15.4	...	5/20/36
	33	16	120	22.0	.....	.....	8.2	9.2	2.0	...	18.6	...	5/21/36

while the qualitative van den Bergh reaction varied from a delayed biphasic to a direct reaction. The three animals in which icterus failed to develop showed considerable hepatic parenchymal destruction, but this destruction was less than that demonstrated in the other animals. The electrolyte pattern in these dogs showed the characteristic alterations, although again to a lesser extent than in the animals in which the liver was more extensively involved. The degree of jaundice was only roughly proportional to the extent of the hepatic damage. Thus, dogs 1, 4 and 10 showed extensive hepatic damage, although the degree of bilirubinemia was much less marked than in the other dogs. The extent of the changes in the electrolytes paralleled the degree of hepatic injury.

TABLE 3.—*Studies of the Blood in Experimental Acute Hepatic Parenchymal Damage*

Dog No.	Erythrocytes, Millions per Cu. Mm.	Hemoglobin, Gm. per 100 Cc.	Vol. of Packed Erythrocytes, Cc. per 100 Cc.	Vol. of Packed Leukocytes and Platelets, Cc. per 100 Cc.	Plasma Volume, Cc. per 100 Cc.	Mean Corpuscular Volume, Cu. Microns	Mean Corpuscular Hemoglobin, Micromicrograms	Mean Corpuscular Hemoglobin Concentration, %	Date	Comments
4	6.27	13.1	42.0	1.1	56.5	67	21	31	12/ 7/34	Control
	7.71	15.5	51.0	0.9	48.1	66	20	30	12/20/34	After 3 repeated doses of arsphenamine
10	5.13	11.0	33.3	1.5	65.2	65	21	33	7/19/35	Control
	6.77	13.6	42.1	1.5	56.4	62	20	32	7/22/35	78 hr. after arsphenamine
12	5.09	10.3	33.1	0.8	66.1	65	20	31	7/24/35	Control
	6.27	14.1	40.4	1.2	58.4	64	22	35	7/26/35	46 hr. after arsphenamine
14	5.61	12.0	36.4	1.5	62.1	65	21	33	7/29/35	Control
	6.38	14.5	41.0	1.8	57.2	64	23	35	7/30/35	25 hr. after arsphenamine
	6.84	14.6	46.2	1.4	52.4	68	21	32	7/31/35	49 hr. after arsphenamine

In all instances there occurred marked hemoconcentration, as determined by hematocrit studies. The reduction of plasma volume varied from 13 to 32 per cent. As is seen in table 3, this reduction in plasma volume was associated with a proportionate increase in the number of red blood cells but with no changes in the character of these cells. The mean corpuscular volume, the mean corpuscular hemoglobin and the hemoglobin concentration remained unaltered throughout the experiments. The hemoconcentration may be explained by the diuresis and to a lesser extent by the diarrhea, which occurred several hours after the administration of arsphenamine and persisted until the time of death.

CHEMICAL STUDIES OF THE BLOOD

Nonprotein Nitrogen and Urea.—Ten of the eleven experimental animals showed a definite increase in the nonprotein nitrogen and urea contents. This increase in the nitrogenous constituents of the blood bore no relationship to the extent of the hepatic damage, as is shown by a comparison of the data for several dogs. In dog 1, in which most of the liver was destroyed, the nonprotein nitrogen and urea contents did not rise to as high a level as they did in dog 12, in which there was comparatively little hepatic damage. Similarly, dog 8 showed a much higher nonprotein nitrogen content than dog 10, although the degree of hepatic damage in the latter was greater than in the former. Two factors probably operated in producing this elevation of the nitrogenous constituents of the blood—the marked dehydration and the failure of renal function.

Sugar.—Three of the eleven dogs showed definite hypoglycemia, the sugar content being 16, 20 and 32 mg. per hundred cubic centimeters, respectively. In the fourth dog the sugar content dropped from 90 to 50 mg. None of the animals showed actual hypoglycemic convulsions. The relationship between the hypoglycemia and the lactic acid content of the blood will be discussed subsequently.

Carbon Dioxide Content.—The nine dogs that died all showed reductions in the carbon dioxide content of the blood in varying degrees. The extent of the reduction was directly related to the degree of elevation of the lactic acid content of the blood and to the extent of the hepatic damage. At no time was acidosis present in the two dogs that recovered.

Sodium.—Four of the eleven dogs showed no change in the sodium content of the serum during the experiment. The remaining four showed a slight drop, varying from 4 to 7.3 milliequivalents per liter.

Chloride.—All the dogs showed a considerable drop in the chloride content of the serum, varying from 7.2 to 20.2 milliequivalents per liter. There was no definite relationship, however, between the degree of the drop in the chloride content and the extent of the hepatic damage. Thus, in dogs 1, 4 and 10, in which the most extensive hepatic changes occurred, the reduction of the chloride content was generally less marked than in the other dogs.

Potassium.—In two of the eight dogs for which potassium determinations were obtained a conspicuous increase in this electrolyte occurred, while in the remaining six animals no appreciable change was evident. In both animals the extent of the hepatic damage was most marked, and the increase in the potassium content of the serum of these dogs (1 and 4) was probably an expression of the extensive cellular destruction of the hepatic parenchyma.

Calcium.—No change in the calcium content of the serum occurred in any of the experiments, this figure remaining remarkably constant.

Phosphorus.—There occurred a considerable increase in the inorganic phosphorus content of the serum of all the nine dogs that died. This increase varied from one and one-half to almost four times the original control value. The increase in phosphorus was roughly proportional to the degree of elevation of nonprotein nitrogen and urea, and these increases in phosphorus failed to take place when no appreciable increase in the nitrogenous elements occurred. Thus, in dog 14 twenty-four hours after the administration of arsphenamine no increase either in the nonprotein nitrogen or in the phosphorus content of the blood occurred, although already there was a considerable elevation in the lactic acid content. Similarly, in the dogs that survived, only a slight increase in the nonprotein nitrogen and urea contents occurred, with no increase in the value for phosphorus. As has been pointed out,[16] this increase in inorganic phosphorus is probably an expression of the failure of renal function.

Magnesium.—For the five animals on which studies of the magnesium content were made, the original control figures were doubled or trebled in three of the four animals that subsequently died, while no elevation of magnesium occurred in the animal that survived. These changes in the magnesium also are probably an expression of renal failure.

Total Protein.—No change in the total protein content was noted in any of the experiments. With the development of considerable hemoconcentration one would expect that a proportionate increase in the protein content would follow. However, that this did not occur is explained by the fact that considerable quantities of protein were lost in the urine.

Lactic Acid.—All of the nine animals that died showed a marked elevation in the lactic acid content of the blood. The increase varied from two to seven times the original control value.

STUDIES OF THE URINE

In two instances (dogs 21 and 24) careful urinary studies were conducted. The animals were placed in metabolism cages and kept there throughout the duration of the experiment.

The specimens of urine were collected under toluene and kept in the refrigerator until aliquots were removed for analysis. The intake of fluid and the output of urine were measured during twenty-four hour periods. The results are recorded in table 4.

16. Marriott, W. M., and Howland, J.: Phosphate Retention as a Factor in the Production of Acidosis in Nephritis, Arch. Int. Med. **18**:708 (Nov.) 1916.

After the administration of arsphenamine there occurred an increase in the output of urine. Only terminally was there actual urinary suppression. With the diuresis there also occurred an increase in the excretion of the lactic acid, while the urinary excretion of chloride and inorganic phosphate was markedly diminished. The latter was due to failure of renal function and probably explains the high level of this electrolyte in the blood. This is further evidenced by the fact that the phosphorus content of the blood increased toward the terminal phase of the experiment, when the nonprotein nitrogen and urea contents were considerably elevated.

TABLE 4.—*Study of the Urine in Experimental Acute Hepatic Parenchymal Damage*

Dog No.	Date (24 Hr. Period)	Fluid Intake, Cc.	Urinary Output, Cc.	Total Protein, Mg. per 100 Cc.	Lactic Acid, Mg. per 100 Cc.	Chloride, Milliequivalents per Liter	Inorganic Phosphate, Mg. per 100 Cc.	Comment
21	10/25 to 10/26	211	311	0	22.0	186.0	73.0	Control
	10/29	...	...	...	....	....	....	65 mg. of arsphenamine per kilogram injected intravenously
	10/29 to 10/30	543	372	160	42.0	26.5	70.2	
	10/30 to 11/1	360	500	420	50.5	14.5	40.0	
24	10/20 to 10/21	200	140	0	15.0	154.0	127.0	Control
	10/21	...	...	...	....	....	....	70 mg. of arsphenamine per kilogram injected intravenously
	10/21 to 10/22	800	460	0	48.8	29.5	78.0	
	10/22 to 10/23	330	500	300	60.6	21.4	40.0	

COMMENT

Certain aspects of this investigation must be borne in mind. These studies represent acute experiments in which hepatic damage was produced suddenly and extensively and in which death occurred within twenty-four to seventy-two hours after the administration of the drug. Arsphenamine, which was used to produce the hepatic parenchymal injury, also produced definite, although slight, renal damage. The electrolyte changes in the blood incidental to the renal damage may, however, be distinguished from changes in the chemistry of the blood which are due to failure of hepatic function.

The most striking changes in the experiments are the hemoconcentration and alterations in the chemistry of the blood. In these alterations the changes of major interest are the acidosis, the hypochloremia, the accumulation of lactic acid in the blood and, incidental

to the latter, the hypoglycemia. The acidosis is due essentially to the increase in lactic acid. The increase in lactic acid is an expression of the failure of the hepatic parenchyma to convert the lactic acid into glycogen. Lactic acid is a normal product of muscular activity, and the phenomena which lead to its appearance have been elucidated by Fletcher and Hopkins,[17] Meyerhof [18] and Hill.[19] During muscular contraction glycogen is decomposed to form lactic acid, and during the recovery phase most of the formed lactic acid is reconverted into glycogen. It must be remembered that the muscles are not the only site of glycogen ⇆ lactic acid transformation. Himwich, Koskoff and Nahum [20] have shown that the venous blood of almost all the organs of the body contains more lactic acid than does the arterial blood. This suggests that the conversion of glycogen into lactic acid and the reconversion of the latter into the former may and do occur anywhere within the body, except in the liver and in the heart. In the liver the lactic acid is removed from the blood stream, converted into glycogen and stored as such. Cori and Cori [21] have shown that the lactic acid content of the blood increases after the injection of epinephrine and that after the injection the hepatic glycogen is increased at the expense of the muscle glycogen. Soskin [22] has shown that epinephrine exercises no effect on the blood sugar of abdominally eviscerated dogs, while Mann and Magath [23] have shown that hepatectomized dogs can succumb to hypoglycemia even when the muscles contain large amounts of glycogen. It becomes evident that muscle glycogen is not directly available for the restoration of blood sugar when the latter becomes depleted but that it must first be converted

17. Fletcher, W. M., and Hopkins, F. G.: The Respiratory Process in Muscle and the Nature of Muscular Motion, Proc. Roy. Soc., London, s.B **89**:444, 1917.

18. Meyerhof, O.: Chemical Dynamics of Life Phenomena, Philadelphia, J. B. Lippincott Company, 1924.

19. Hill, A. V.: The Mechanism of Muscular Contraction, Physiol. Rev. **2**:310, 1922.

20. Himwich, H. E.; Koskoff, Y. D., and Nahum, L. H.: Changes in Lactic Acid and Glucose in the Blood on Passage Through the Organs, Proc. Soc. Exper. Biol. & Med. **25**:347, 1928.

21. Cori, C. F.: The Influence of Insulin and Epinephrine on the Lactic Acid Content of Blood and Tissues, J. Biol. Chem. **63**:253, 1925. Cori, C. F., and Cori, G. T.: The Mechanism of Epinephrine Action: I. The Influence of Epinephrine on the Carbohydrate Metabolism of Fasting Rats, with a Note on New Formation of Carbohydrates, ibid. **79**:309, 1928.

22. Soskin, S.: Muscle Glycogen as a Source of Blood Sugar, Am. J. Physiol. **81**:382, 1927.

23. Mann, F. C., and Magath, T. B.: Studies on the Physiology of the Liver: III. The Effect of Administration of Glucose in the Condition Following Total Extirpation of the Liver, Arch. Int. Med. **30**:171 (Aug.) 1922.

into lactic acid, which is reconverted into glycogen, mostly by the liver, and then becomes available as a source of blood sugar.

In the light of this explanation the reason for the accumulation of lactic acid in the blood in our experiments becomes evident. The development of hypoglycemia in four of the experimental animals is readily explained by the inability of the liver to convert lactic acid into glycogen and hence a lack of available glycogen to be converted into dextrose when the need arises.

The increase in the lactic acid content of the blood is roughly proportional to the extent of the damage to the liver.

In dogs 3 and 18, which survived, no increase in the lactic acid content of the blood occurred, despite the fact that the animals showed icterus that was apparently indicative of some hepatic parenchymal damage. One of these animals showed some hemoconcentration and hypochloremia. The other electrolytes were entirely normal.

The relationship between the hypochloremia and the hepatic and renal damage is more complex. Hypochloremia commonly occurs in the terminal stages of nephritis. Trusler, Fisher and Richardson [24] have explained the low values for blood chloride in dogs poisoned with mercury bichloride as due to the severe vomiting and diarrhea which follow the administration of the poison. However, in interpreting the results of our series of experiments it must be remembered that vomiting occurred only directly after the administration of the arsphenamine, while diarrhea, although present, was at no time pronounced.

It may be that the drop in the chloride value represents an effort toward chemical adjustment in the serum. Atchley and Benedict [25] have shown that after ligation of the ureters of the dog there occurs a decrease in the carbonate and chloride contents of the blood which is equal to the increase in inorganic phosphate and sulfate.

SUMMARY

Studies of the electrolytes of the blood and urine are reported for dogs in which acute diffuse hepatic parenchymal damage was produced by the intravenous injection of arsphenamine.

The most outstanding changes consisted of pronounced hemoconcentration, a drop in the chloride and carbonate contents and an increase in the inorganic phosphate and lactic acid contents of the serum. In

24. Trusler, H. M.; Fisher, W. S., and Richardson, C. L.: Chemical Changes in the Blood in Mercuric Chloride Poisoning: Mechanism and Significance of Hypochloremia, Arch. Int. Med. **41**:234 (Feb.) 1928.

25. Atchley, D. W., and Benedict, E. M.: The Distribution of Electrolytes in Dogs Following Ligation of Both Ureters, J. Biol. Chem. **73**:1, 1927.

three of the eleven dogs severe hypoglycemia developed. The reasons for the accumulation of lactic acid in the blood and the mechanism of the development of the hypoglycemia are described. While the latter changes are due to hepatic injury, increase in the blood phosphate probably represents a manifestation of failing renal function. The reasons for the drop in the chloride value are less clear. The vomiting was not severe enough to explain the considerable drop which occurred in this electrolyte.

A slight drop in the sodium content of the serum occurred in four of the seven animals. Two animals showed a considerable increase in serum potassium, while none of the animals showed any changes in the serum calcium.

After the administration of arsphenamine there occurred an increase in the volume of urine, with a considerable increase in the urinary excretion of lactic acid and total protein, while there was a marked reduction in the excretion of chloride and inorganic phosphate.

Progress in Internal Medicine

PERIPHERAL VASCULAR DISEASES

A REVIEW OF SOME OF THE RECENT LITERATURE AND A CRITICAL REVIEW OF THE SURGICAL TREATMENT

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CHICAGO

A REVIEW OF SOME OF THE RECENT LITERATURE

By Dr. Scupham

It has become noticeable, particularly in the last year, that interest in disorders of the blood vessels of the extremities is no longer confined to special groups working in large centers of population. The great number of papers appearing on this subject from all parts of this country and of the world are evidence of the widespread interest and appreciation of the importance of a subject which only in the last few years has become generally recognized. Many of these papers are case reports or short articles on diagnosis and treatment and consist of brief summaries of generally accepted methods.

The painstaking and careful work of many years on the physiology both normal and abnormal of the blood vessels by Sir Thomas Lewis [1] has been embodied in practical form in a small volume entitled "Vascular Disorders of the Limbs." This book is a summary of the views of this author, written in his usual simple and expressive style, and covers the disorders of the blood vessels of the extremities. It has been written for students and practitioners, and the author's views are expressed briefly and concisely. No attempt will be made to review this volume or many of the papers which have appeared during the past year. Some of the more significant ones or those which seem to emphasize some important feature will be included.

1. Lewis, Thomas: Vascular Disorders of the Limbs Described for Practitioners and Students, New York, The Macmillan Company, 1936.

GLOMUS TUMORS

In a previous review [2] the subject of the arteriovenous anastomoses between the arterioles and the venules in the skin, particularly the work of Popoff, was reviewed. At that time no mention was made of the glomus tumor. Reports of this type of new growth have been occasional for many years. Several papers have appeared recently which again draw attention to this condition and clarify the clinical and pathologic aspects of this peculiar new growth which arises from the Suquet-Hoyer canals.

Theis [3] briefly reviews the literature on this subject and reports a case of subungual neuromyo-arterial glomus tumor of the toe occurring in a patient treated for arteriosclerosis obliterans by suction and pressure therapy. The author's observations and comment are in essential agreement with those of Chiari.[4] Pain is the outstanding symptom, and Chiari emphasizes it as being exceedingly severe, sharp and burning. It may radiate up the entire extremity, so that when the tumor is located on a finger the pain may extend into the shoulder and even into the neck. The pain is dependent on distention of the tumor mass, with blood filling the small channels and thus causing pressure on the numerous small nerve fibers which make up a large part of the matrix of the growth. Pain is intensified by heat, and in Theis' patient it became much more marked after alternating pressure and suction treatment, when the circulation was improved. Cold and pressure on the tumor may shunt the flow of blood outside through collateral channels. Pain is then relieved.

These tumors are small, seldom being more than a few millimeters in diameter. They are located on the hands and feet, a few of them being subungual. Others appear on the palms or soles and some higher on the extremities. They are bluish red when filled with blood and present many of the characteristics of a varix. Chiari states that they occur with equal frequency in males and females. The ages of the patients vary from childhood to senility. Trauma has been designated as being an important factor. The tumors seem never to be malignant, and no recurrences after excision have been reported. Chiari states that the tumors show the characteristic vessels of the normal glomus structure but are dilated and filled with blood. They are thick walled,

2. Scupham, George W., and de Takáts, Géza: Peripheral Vascular Diseases: A Review of Some of the Recent Literature, with a Critical Review of Surgical Treatment, Arch. Int. Med. **58**:531 (Sept.) 1936.

3. Theis, Frank V.: Subungual Neuromyo-Arterial Glomus Tumor of the Toe, Arch. Surg. **34**:1 (Jan.) 1937.

4. Chiari, H.: Zur Pathologie der peripheren Gefässe, Wien. klin. Wchnschr. **50**:395 (March 26) 1937.

with large cells and occasional typical smooth muscle fibers. The type of cell may vary considerably in different specimens. In some the endothelial cells predominate, and in others the matrix of the tumor is largely made up of muscle fibers or elastic fibers through which pass numerous nerve fibers. In some instances the growth resembles an endothelioma and in others a myoma.

CAPILLARIES

Roboz [5] has attempted the use of a method for measuring capillary function which he calls the vasothermal capillary reaction. He measured the flow of blood in the capillaries of the nail bed at room temperature and after immersion of the hand in water at 50 C. Distinct types of reactions in the capillaries were noted. The typical reaction occurred in the majority of persons observed. In these the circulation time after immersion in warm water increased so much that during a ten minute period of observation the capillary blood flow could not be measured. In the atypical type of reaction the speed of the corpuscular stream through the capillaries became measureable in four minutes or less. In a few instances there was a paradoxic reaction, in which the stream of corpuscles came to a standstill after exposure to heat. Roboz found that when the capillary bed was typical morphologically, the reaction was always typical. The converse was also true. When the functional test gave an atypical reaction there was an atypical capillary pattern. This reaction is likewise dependent on the functional state of the capillary wall, particularly in regard to its tonus. In acrocyanosis the corpuscular stream was stationary at room temperature and never reached the proportions of the typical reaction. In four persons who stammered, variable circulation times were noted in different capillaries. These variations seemed to be characteristic in other types of vasoneuroses. The value of this type of observation is not yet established, but further studies may throw light on some of the minor functional disturbances of circulation in the hands and feet about which relatively little is known.

INTERMITTENT CLAUDICATION

The reason for the development of pain in muscles which are deprived of adequate blood supply has been a matter of speculation for many years. Numerous theories have been advanced, most of them to be disproved. Veal and McFetridge [6] made an arteriographic study

5. Roboz, P.: Beiträge zur Funktionsprüfung der Capillaren, Klin. Wchnschr. **15**:968 (July 4) 1936.

6. Veal, J. Ross, and McFetridge, E. M.: Vascular Changes in Intermittent Claudication, with a Note on the Value of Arteriography in This Symptom Complex, Am. J. M. Sc. **192**:113, 1936.

of a group of patients with intermittent claudication and found no evidence of vascular change either after an attack, when pain was at its height, or after treatment of the condition, when the subjective state of the patient was much improved. These authors feel that arterial spasm plays no part in the condition.

The views of Lewis and his associates are generally accepted as the best explanation for the phenomenon.

Elliott and Evans [7] have attempted to confirm the view that the substance released by muscle activity which is responsible for the production of pain by its effect on nerve endings in the muscles is probably the lactate ion or a substance the metabolism of which is closely related to that of lactic acid. They believe that this hypothesis explains the experimental results which they obtained and that the production and disposal of lactic acid and the "pain substance" are subject to similar metabolic laws. Experiments were conducted on healthy young adults with the blood supply to the arm occluded by pressure of 200 mm. of mercury. They found that the presence of lactic acid in the blood, whether produced by exercise, epinephrine or sodium lactate, was regularly accompanied with an earlier appearance of ischemic pain in the muscles of the forearm than in those of the controls. This effect usually outlasted the rise in the lactic acid content of the blood, but in no instance did exercise tolerance return to normal in the phase of continuing acidemia. Decreased exercise tolerance of the forearm often occurred without a rise in the lactic acid content of the blood. The authors explain that the lactic acid content of muscles about the nerve endings may remain elevated while the value for the blood returns to normal. The typical course of events in most of their experiments was a rapid drop in exercise tolerance during the first fifteen to thirty minutes of induced acidemia. When the diffusion rate is rapid, this is followed by flattening out of the curve of exercise tolerance as diffusion from blood to tissues becomes slow. A gradual recovery by the reversal of the direction of diffusion occurs after the concentration of the blood has fallen to normal.

The authors state that some of their observations are not in strict agreement with the hypothesis that lactic acid is the sole substance responsible for ischemic muscle pain. In these experiments no rise in the lactic acid content of the blood was encountered, but the decrease in exercise tolerance was consistent and unmistakable and was comparable with that occurring from induced acidemia. These results followed exercise of the legs and the trapping of the "pain substance"

7. Elliott, A. H., and Evans, R. D.: Ischemic Pain in Exercising Muscles, Am. Heart J. **12**:674, 1936.

in the forearm after its release from the legs. They think this may indicate that another substance or other substances may be capable of producing ischemic pain.

DIAGNOSTIC METHODS

Methods for the diagnosis of peripheral vascular disease have been so well established that relatively little has been added during the past year. The large number of papers reporting on these conditions are summaries of previous and now generally accepted work.

Battro and Lanari,[8] however, suggest the use of acetylcholine by intra-arterial injection as an excellent, simple and harmless test to differentiate functional and organic disturbances. In functional disturbances the changes following the injection of acetylcholine do not differ from those noted in normal persons. In the presence of organic lesions when the main artery is occluded, the oscillographic findings remain unchanged below the site of the occlusion. The status of the collateral circulation is gaged by the degree, distribution and rapidity of appearance of the change in color which occurs after the injection of acetylcholine. This likewise furnishes information as to the site for amputation. It may be that this method for the release of vascular tone is of some importance. It is at least as difficult as the nerve block procedure and certainly no more effective. It surely carries greater possibility for unfavorable consequences.

Collens and Wilensky[9] report two objective tests for the measurement of peripheral vascular obstruction. One of these tests measures the claudication time and the other the venous filling time. The latter test is carried out by placing the patient in a recumbent position with one foot or hand elevated as high as possible. The patient then alternately flexes and extends the digits until blanching occurs. The extremity is then lowered below the level of the bed. The veins are collapsed. The time required for the blood to show the first sign of distending the vein is noted. Normally this is in from seven to ten seconds; in patients with pathologic conditions it has been noted to extend as long as two minutes. The longer the filling time, the greater the degree of vascular obstruction.

Measurements of the temperature of the skin remain the most widely accepted measurement of the peripheral blood flow.

Arteriography.—Most workers in the field of arteriography seem to have arrived at similar conclusions in regard to the value of this

8. Battro, A., and Lanari, A.: Inyección intraarterial de acetilcolina; su valor diagnóstico en las afecciones vasculares periféricas, Rev. argent. de cardiol. **3**:31, 1936.

9. Collens, William S., and Wilensky, Nathan D.: Two Quantitative Tests of Peripheral Vascular Obstruction, Am. J. Surg. **34**:71, 1936.

method. As recorded in previous reviews, the characteristic appearances of the arteriographic picture in several pathologic disorders as well as in the normal state are distinct. Certain precautions in regard to interpretation are stressed by Yater [10] and by Allen.[11] This is particularly true in regard to colloidal thorium dioxide, which, when injected into the blood stream, rapidly leaves the vascular system, so that the time between the injection and the exposure of the film must be brief. In some instances complete filling of the distal arteries may not have occurred and may lead to errors in diagnosis. This happens particularly if the exposure has been made too quickly, or it may be due to other variations in technic. Thorium dioxide is the substance which is almost universally used in this country. While there still seems to be some doubt as to the possibility of latent damage from the use of a radio-active substance, up to this time no bad effects have been recorded in this country. Yater,[10] in his excellent paper, discusses the form of the normal arteriogram as well as that seen in patients with typical disease conditions. His ideas agree with those of others previously reported. He states that though there may be many variations of the normal vascular tree of the extremities, the main arteries usually conform to a standard pattern. Owing to the state of the circulation and the lag in the diffusion of thorium dioxide, only a certain number of vessels are made visible at the same time. This is characteristic of the normal arteriogram, in which the arteries appear to be smooth walled and to have a relatively direct course. The fact that the normal arteriogram shows only the larger and more direct vessels probably explains why it is that these are the ones usually affected by degeneration. They bear the brunt of the circulatory load, and this factor of stress is important in the localization of degenerative disease. The smaller vessels and branches are often less severely affected and take up the function of the collateral circulation.

The description that Yater gives of arteriosclerosis and thrombo-angiitis obliterans is essentially the same as that recorded in previous reviews. He states that arteriography shows that thrombo-angiitis obliterans is a polyphasic disease, in that various stages are present in the various arteries and their branches at the same time. Disease of the collateral circulation is the most extensive of all vascular diseases. The author notes that arterial spasm of a severe type may occur with arterial puncture in this condition as well as in Raynaud's disease.

10. Yater, Wallace M.: Thorotrast Arteriography of the Extremities, with Report of Illustrative and Unusual Cases, Am. Heart J. **12**:383, 1936.

11. Allen, E. V.: The Peripheral Arteries in Raynaud's Disease: An Arteriographic Study of Living Subjects, Proc. Staff Meet., Mayo Clin. **12**:187 (March 24) 1937.

Arteriovenous fistula and aneurysm can be well demonstrated. He emphasizes that the importance of arteriography is in selecting the best site for amputation. He agrees with others that it affords an excellent method for study of vascular disease in living subjects, but he does not regard it as a necessary diagnostic procedure except in cases in which the clinical diagnosis is difficult.

This is emphasized in the report of a case by Baker and Allen,[12] in which the diagnosis of the disease was not apparent on clinical examination. In this case the arteriogram was characteristic of thromboangiitis obliterans and served to confirm the clinical diagnosis.

Allen [11] made a study of 22 patients with Raynaud's disease who showed all the symptoms pointing to a diagnosis of this condition. He summarizes the findings as follows: "There was an absence of filling of the radial arteries in two cases, normal filling of all arteries in four cases, absence of filling of the digital portions of more than one or two digital arteries in sixteen cases, and small caliber of some or all the digital arteries in eighteen cases." He does not consider incomplete filling of the digital portions of the digital arteries as evidence of inherent arterial disease. It seems to indicate a functional disorder. Arteriograms were also made for asthenic persons who did not have Raynaud's disease. The appearance of the arteriograms in these instances was the same as that noted in Raynaud's disease. After removal of the cervical thoracic sympathetic ganglions in Raynaud's disease arteriograms may or may not produce normal filling of digital arteries which did not fill normally before operation. The author concludes that if a local fault is responsible for Raynaud's disease, it does not appear in arteriograms to be organic.

Ratschow [13] agrees that the importance of arteriography lies principally in the estimate it allows of the efficiency of the peripheral circulation, in regard to both the arteriogram and the venogram. He thinks that the method has made it possible to demonstrate the various factors which influence the flow of blood in the veins. The efficiency of the compensating channels in a patient with varicose veins can be determined to much better advantage than by any other method. The same applies to the collateral circulation in regard to selection of the site for amputation. The author's work has been with neo-iopax and abrodil (the sodium salt of mono-iodomethane sulfonic acid). These substances

12. Baker, T. W., and Allen E. V.: Diagnostic Value of Arteriography: Report of a Case, Proc. Staff Meet., Mayo Clin. **11**:500 (Aug. 5) 1936.

13. Ratschow, M.: Leistung und Bedeutung der Vasographie als Funktionsprüfung der peripheren Blutgefässe, Fortschr. a. d. Geb. d. Röntgenstrahlen **55**: 253, 1937.

have been shown to be satisfactory, particularly for venography. The pain produced by the intra-arterial injection of the substances is difficult to explain. It can largely be minimized by the periarterial injection of procaine hydrochloride at the site of the puncture. In arteriograms made serially he has been able to follow the contrast medium to the smallest vascular branches.

Veal and McFetridge [6] have made an arteriographic study of intermittent claudication in 15 carefully selected patients. Syphilis and thrombo-angiitis obliterans were eliminated. In 12 the cause was arteriosclerosis, and in 3 others the etiologic basis could not be determined. Thorium dioxide was the contrast medium used. The authors were able to divide the patients into three distinct groups. The first included those in whom the cause was arteriosclerosis and in whom the most outstanding change was obliteration of the large arteries. There was a diminution in the number of large muscular branches, and their distribution was uneven and clearly inadequate. In the second group of arteriosclerotic patients the large arteries were not obliterated, but their lumens were narrowed. There was also a marked diminution in the size of the muscular branches and in the number of small terminal vessels. The third group included those for whom a diagnosis could not be made. The arteriograms showed no change in the main arteries in 1 patient, narrowing of the popliteal and tibial arteries was noted in the second and complete occlusion of the popliteal artery was noted in the third. The characteristic finding in all 3 patients was a peculiar clubbing and dilatation of the muscular branches, which terminated abruptly.

With exercise and the appearance of intermittent claudication, it was not possible to show any decrease in the size of the vessels or in the form of the arteriogram, except that the vessels in some instances appeared to be actually dilated. In 1 patient the improvement in the clinical condition which followed treatment could not be correlated with any change in the form of the arteriogram. The authors are certain that intermittent claudication could not have been due to arterial spasm, from the evidence produced by arteriography. They believe that the method is a valuable means of making a definite diagnosis in cases of pain in the extremities in which a vascular lesion may not be evident.

Veal and McCord [14] emphasize the value of arteriography in the diagnosis of abnormal arteriovenous communications in the extremities. It is the only method by which the number, location, type and size of the communicating passages may be demonstrated.

14. Veal, J. Ross, and McCord, William M.: Congenital Abnormal Arteriovenous Anastomoses of the Extremities, with Special Reference to Diagnosis by Arteriography and by Oxygen Saturation Test, Arch. Surg. **33**:848 (Nov.) 1936

THROMBO-ANGIITIS OBLITERANS

The fact that the pathologic characteristic of thrombo-angiitis obliterans presents the picture of an inflammatory process has led most workers to believe that this disease is actually a bacterial inflammatory condition. No absolutely conclusive proof has been brought to bear on this subject. There has been considerable difficulty in transmitting the infection to experimental animals. A case of accidental transmission of the disease from man to man has been reported by Allen and Lauderdale.[15] They review the literature on this subject and report the case of a surgeon 45 years of age who, while amputating the toe of a man with thrombo-angiitis obliterans, accidentally suffered a wound of a finger by a spicule of bone from the patient's toe. One month later color changes, consisting of cyanosis and pallor on exposure to cold, appeared in this finger and somewhat later two other fingers of the same hand became involved. Examination six months later revealed a reduction in the cutaneous temperature and abnormal pallor of these fingers. The temperature of these digits after ingestion of ethyl alcohol remained below that of the other hand. From the clinical findings it seems that the diagnosis in this case was correct and that it is highly probable that the disease resulted from transmission of the infection rather than being a mere coincidence.

Friedlander, Laskey and Silbert[16] have continued their work on the relation of blood volume to endocrine function. Part of this material was reviewed last year. In an additional paper they discuss the effect of estrogenic substance on blood volume. Study revealed a consistent rise in blood volume to normal levels after treatment with estrogenic substance in all groups of patients in whom the initial blood volume was low. The reduction in blood volume which follows bilateral oophorectomy was compensated for in 5 patients who were given estrogenic substance. In 7 men with thrombo-angiitis obliterans the same result was obtained, while in 2 normal women who showed a normal initial blood volume and in 4 normal cats no changes were produced. Male cats which had been subjected to thyroidectomy likewise showed a reduction in blood volume, which could be restored to normal by administration of the hormone. While no absolute conclusion can be drawn from this work, it may be of some importance in explaining the reason for the relative infrequency of the disease in females.

15. Allen, E. V., and Lauderdale, T. L.: Accidental Transmission of Thrombo-Angiitis Obliterans from Man to Man, Proc. Staff Meet., Mayo Clin. **11**:641 (Oct. 7) 1936.

16. Friedlander, Mae; Laskey, Norman, and Silbert, Samuel: Effect of Estrogenic Substance on Blood Volume, Endocrinology **20**:329, 1936.

Two cases of thrombo-angiitis obliterans in women have been reported. One of these is reported by Herrell and Allen,[17] who comment again on the rarity of the disease in women. They conclude that there is considerable question of the diagnosis in several of the cases that have been reported. Their patient was a Scandinavian woman aged 41, who presented characteristic vasomotor disturbances and typical intermittent claudication. Occlusion of the larger arteries of the leg and superficial phlebitis were observed. The disease was progressive and arteriosclerosis could not be demonstrated. The patient used tobacco excessively. The authors believe the criteria for the diagnosis of the disease has been fulfilled. Van Dellen and Wright [18] report the case of a Russian Jewess of 46 who likewise presented symptoms and findings which could be considered characteristic of the disease. It is to be noted that in both cases, as in most of the others reported in women, the disease was relatively mild and seemed to respond fairly well to therapy.

Several interesting cases of the disease in Negroes have been reported in the last year. Parson [19] describes a case in a man who was five-eighths white. This seems to be an authentic case, although the patient had syphilis and pathologic confirmation is lacking. Smith [20] describes another case in a Negro, and Yater [21] reports 5 additional cases which seem to fulfil the requirements for the diagnosis of this disease. The patients were all full-blooded Negroes, as nearly as could be determined. Pathologic and arteriographic examinations confirmed the diagnosis. All the men had syphilis, but Yater states that the incidence of the disease in Negroes is so high that the association of the two conditions may have been purely accidental. Pathologically the lesions were not suggestive of syphilis, nor is syphilis of the medium-sized arteries at all common. Yet Yater does not exclude the possibility that there may be some causal relationship.

Further studies on the effect of tobacco on the cardiovascular system have been made by Maddock, Malcolm and Coller.[22] They found no relationship between cutaneous sensitivity to tobacco and the fall in temperature of the digits and the rise in blood pressure with smoking.

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17. Herrell, Wallace E., and Allen, Edgar V.: Thrombo-Angiitis Obliterans in Women: Report of a Case, Am. Heart J. **12**:105, 1936.

18. Van Dellen, T. R., and Wright, I. S.: Thrombo-Angiitis Obliterans in Women: Report of a Case, Am. Heart J. **13**:373, 1937.

19. Parson, G. W.: Case of Thrombo-Angiitis Obliterans in Negroid, Texas State J. Med. **32**:546, 1936.

20. Smith, C. A.: Thrombo-Angiitis Obliterans: Report of a Case in Negro, Texas State J. Med. **32**:462, 1936.

21. Yater, Wallace M.: Thrombo-Angiitis Obliterans in Negroes, Am. Heart J. **13**:511, 1937.

22. Maddock, Walter G.; Malcolm, Russell L., and Coller, Frederick A.: Thrombo-Angiitis Obliterans and Tobacco, Am. Heart J. **12**:46, 1936.

The effects of cigaret smoking were observed on both men and women, and the results were essentially the same; the reductions in the temperature of the digits with increases in blood pressure and in pulse rate were similar in the two sexes. Similar experiments carried on with Jews showed a greater drop in the temperature of the fingers than occurred in gentiles. The authors think that this may account for the greater incidence of thrombo-angiitis obliterans among Jews than among other elements of the population. No explanation of this fact is offered. The authors feel that cigaret smoking definitely reduces the blood supply to the extremities and for this reason is an important predisposing factor in the development of thrombo-angiitis obliterans.

Ratschow [23] investigated the effect of exposure to cold and wet as an etiologic factor in peripheral vascular diseases. In thrombo-angiitis obliterans as well as in other circulatory disorders he found that occupation was not an important factor. Study of the disease among men and women engaged in the fishing industry, in which exposure to cold and water is excessive, showed that there has not been a single case in four years.

All the patients with thrombo-angiitis obliterans were divided into five groups according to occupation: (1) sedentary occupations without exposure (23 men), (2) manual labor without exposure (38 men), (3) light labor with occasional exposure to cold (20 men), (4) hard labor with occasional exposure (17 men) and (5) hard labor with constant exposure to cold and wetness (11 men). He points out that while exposure plays no part as an etiologic factor, there is a constitutional vascular defect which is the probable underlying cause.

In discussing thrombo-angiitis obliterans Yanovsky [24] says he considers that the disease should be called neuro-angiitis obliterans, because of the involvement of the sympathetic nerves and blood vessels in the pathologic process. He emphasizes the importance of the involvement of the sympathetic nerves, particularly the sympathetic fibers in the adventitia. Degeneration of these fibers occurs as the result of the inflammatory process and fibrosis. The author considers the formation of the thrombus merely the result of damage to the intima and believes it is not specific in the disease.

Braeucker [25] expresses a somewhat similar view. He believes that the inflammatory process in the wall of the vessel results in irritation

23. Ratschow, M.: Periphere Durchblutungsstörungen und Berufsschäden, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1936, p. 220.

24. Yanovsky, M.: Sistema neuro-organo-vegetativo en el sindrome trombo-angiitis tipo buerger, denominado neuroangiitis fibrosa obliterante, Semana méd. 2: 968 (Oct. 8) 1936.

25. Braeucker, W.: Die Heilerfolge bei den Gefässerkrankungen an den Extremitäten, Verhandl. d. deutsch. Gesellsch. f. Kreislaufforsch., 1936, p. 319.

of the adjacent nerve plexuses. Abnormal nerve impulses are initiated which result in reflex vasoconstriction. These views are not entirely new, but the emphasis which Yanovsky places on the involvement of the sympathetic fibers within the vascular walls may be important.

Parker and Allen [26] report an interesting case of an inflammatory disease involving the digital arteries in which there were the clinical characteristics of Raynaud's disease. They believe this was actually a case of thrombo-angiitis obliterans.

Bircher [27] describes a typical case of this disease in which he believes alimentary intoxication and vitamin deficiency played important parts in the etiology. He seems to base these conclusions on the effects of treatment. He likewise considers the effect of tobacco and secondary infection of the gangrenous areas as important contributing etiologic factors in the subsequent course.

Telford,[28] in a general discussion of the condition, also emphasizes the fact that the typical pathologic condition may be obscured by a secondary infection which occurs in ulcers in gangrenous areas. He considers the disease rare in the upper extremities and comments on the fact that when the hands are involved the disease has usually made great progress in the legs.

The visceral manifestations of the disease continue to arouse considerable interest. Telford [28] cites again the case of a man aged 26 who died of coronary thrombosis and whose coronary arteries showed typical pathologic signs of thrombo-angiitis obliterans. Cohen and Barron [29] review the literature on this subject and comment on the paucity of actual autopsy material. They found reports of only 15 cases in which thrombo-angiitis obliterans involving the digestive tract was suggestive. In 2 of these the diagnosis was proved, in 2 it was doubtful and in the others it was presumptive. The authors believe that associated arteriosclerosis may replace the typical pathologic picture and that degenerative changes often take place in the vessels when the disease process is primarily that of thrombo-angiitis obliterans. They report an additional case of presumptive thrombo-angiitis obliterans in which the peripheral

26. Parker, R. L., and Allen, E. V.: Organic Disease of the Digital Arteries Suggesting Thrombo-Angiitis Obliterans and with the Clinical Features of Raynaud's Disease, Proc. Staff Meet., Mayo Clin. **12**:118 (Feb. 24) 1937.

27. Bircher, Willy: Ein Fall von Endarteriitis obliterans, München. med. Wchnschr. **84**:168 (Jan. 29) 1937.

28. Telford, E. D.: Thrombo-Angiitis Obliterans, Lancet **1**:549 (March 6) 1937.

29. Cohen, S. S., and Barron, M. E.: Thrombo-Angiitis Obliterans with Special Reference to Its Abdominal Manifestations, New England J. Med. **214**:1275 (June 25) 1936.

findings were conclusive; at operation the condition within the abdomen suggested the diagnosis but did not offer definite proof. The clinical picture was that of partial intestinal obstruction, colicky abdominal pain, vomiting, obstipation, distention and fever. These symptoms they regard as highly suggestive of involvement of the mesenteric vessels in the presence of peripheral disease. They believe that this condition should be considered an entity.

Saphir [30] reviews the literature reporting the autopsy observations in instances of Buerger's disease and notes the frequency, as have others, of the occurrence of coronary sclerosis and the relatively few patients who actually show the characteristic pathologic picture of thrombo-angiitis obliterans. The patient whose case he describes in detail was a 35 year old man who died suddenly after an acute infection of the respiratory tract. For six years he had had symptoms of arterial disease involving the lower extremities but no evidence of cardiac disease. The autopsy revealed the combined picture of acute thrombo-angiitis obliterans and arteriosclerosis. There were apparent transitions from the former to the latter, rendering it difficult to differentiate a thrombus arising on an atheromatous basis and a later stage of thrombo-angiitis obliterans when organization of the thrombus had taken place. It seemed questionable whether the association of the two diseases was merely coincidental or the coronary sclerosis was the end-stage of earlier thrombo-angiitis obliterans or had developed as an entirely different entity on the basis of thrombo-angiitis obliterans. Saphir considers it possible that the inflammatory lesion in the vessel may have been a factor at least in the causation of the coronary sclerosis. This view has been expressed before, and Saphir's careful study lends weight to this opinion.

The coincidence of thrombo-angiitis obliterans and Addison's disease in the same patient is reported by Silbert.[31] He raises the question of the possibility that the adrenal impairment is due to the vascular disease but concludes that this is not likely, because he considers visceral involvement a late manifestation of thrombo-angiitis obliterans.

Kvale and Allen [32] reviewed reports on 255 patients with thrombo-angiitis obliterans and found that sudden arterial occlusion in the extremities appeared as the initial symptom of the disease in 11. It developed at various times during the course of the disease in 15 other patients in 10 of whom it was of such serious nature that amputation

30. Saphir, Otto: Thromboangiitis Obliterans of the Coronary Arteries and Its Relation to Arteriosclerosis, Am. Heart J. **12**:521, 1936.

31. Silbert, Samuel: Thrombo-Angiitis Obliterans and Addison's Disease in the Same Patient, J. A. M. A. **108**:551 (Feb. 13) 1937.

32. Kvale, Walter, and Allen, Edgar V.: Sudden Arterial Occlusion in Thromboangiitis Obliterans, Am. Heart J. **12**:458, 1936.

was eventually necessary. The authors point out that the serious consequences of this complication are due to the fact that the blood supply has been previously so reduced that the limb cannot survive further reduction. As they point out, this complication has been emphasized by Buerger and others.

The patient described by McAuley [33] probably falls into the group presenting sudden occlusion as the initial symptom. The first symptoms of the disease in this patient appeared within twenty-four hours. The foot began to feel numb and cold in the morning and later in the day became extremely painful. The subsequent course was that of the rapid development of typical symptoms.

SPECIFIC AND NONSPECIFIC TYPES OF ARTERITIS

Periarteritis nodosa continues to be a disease of considerable interest. Case reports have been more frequent. The etiology is still uncertain.

Spiegel [34] reports on a series of 15 patients, giving the postmortem observations. More than half the patients had preceding illnesses in which hemolytic streptococci were the most common bacterial agents implicated. These illnesses included tonsillitis, sinusitis, scarlet fever, asthma and rheumatic fever. The usual histologic picture of widespread vascular reactions prevailed. Seven patients in the group had surgical complications involving the gastro-intestinal tract. Almost all had abdominal pain. The coronary arteries, as stated in previous reports, seemed to be most frequently affected. Twelve patients had polyserositis, and high leukocyte counts were noted (in 1 patient, 54,000). The predominating cell was the polymorphonuclear leukocyte, although strikingly high eosinophil counts sometimes were noted. Healing and prolonged remissions occurred. Cutaneous lesions were not uncommon. The disease ocurred in association with gonococcic infection and meningitis in 1 case. Only 1 of the patients in this series showed typical manifestations of an allergic state. Cohen, Kline and Young,[35] in a discussion of this condition, report 3 additional cases in which severe asthma was a predominating symptom. They believe that periarteritis nodosa is a severe manifestation of clinical allergy.

The pathologic picture, in their opinion, is not to be distinguished from that of severe allergy in which reversible reactions of varying degrees and irreversible reactions occur. There are areas of scarring

33. McAuley, C. J.: Thrombo-Angiitis Obliterans, Brit. M. J. **1**:411 (Feb. 20) 1937.

34. Spiegel, Rose: Clinical Aspects of Periarteritis Nodosa, Arch. Int. Med. **58**:993 (Dec.) 1936.

35. Cohen, M. B.; Kline, B. S., and Young, A. M.: The Clinical Diagnosis of Periarteritis Nodosa, J. A. M. A. **107**:1555 (Nov. 7) 1936.

alone, areas in which only allergic inflammation are noted and every conceivable combination of allergic inflammation and repair. They divide the patients into four general groups according to the symptomatology: (1) fever, splenomegaly, leukocytosis, severe anemia and marked emaciation, (2) polyneuritis and polymyositis, (3) renal type and (4) abdominal type, with epigastric pain, vomiting and diarrhea. Combinations of these often occur, but some one group seems frequently to predominate. They state: "The clinical diagnosis is not difficult to make if the clinician will consider every patient having severe allergy as presenting a potential case of periarteritis nodosa and will watch for symptoms and signs which may be explained on the basis of a temporary or permanent disturbance of the blood supply to an organ."

Boyd and Nussbaum,[36] in a general discussion of the disease, emphasize the widespread vascular involvement and the multiplicity of symptoms. They noted that bronchial asthma is often recorded in the previous illnesses. Gonococcic infections in a few instances seem to them to possess etiologic significance, but syphilis is no longer to be regarded as a factor. Inability to discover the etiology of suspected sepsis together with negative results of blood culture is suggestive of periarteritis nodosa.

Yardumian and Cohen [37] present the case of a woman aged 64 whose chief complaint was of pain in the legs for the preceding two months. The pain was bilateral below the knees and cramplike, but was present only when the legs were dependent, always disappearing when the legs were elevated. There were no changes in the color or temperature of the skin. This patient also had had asthmatic symptoms during previous years. Autopsy confirmed the diagnosis. In 1 of the cases reported by Cohen, Kline and Young a diagnosis of Raynaud's disease had previously been made, and periarterial sympathectomy had been performed. Bilateral cervical sympathectomy was performed later, and one thumb and the gangrenous tips of two fingers were removed.

The relation of allergy to this condition is interesting, and the frequency with which allergic states are mentioned in the histories has been suggestive.

Spiegel in 1 patient with asthma observed at necropsy multiple pulmonary infarcts due to small thrombosed vessels in the lungs which might be held accountable for the asthma. She questions whether allergy on a nonbacterial basis may be associated with the development of periarteritis nodosa.

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36. Boyd, L. J., and Nussbaum, C.: Some Clinical Aspects of Periarteritis Nodosa, M. Clin. North America **20**:973, 1936.

37. Yardumian, K., and Cohen, R. Robert: Periarteritis Nodosa with a Case Report, Ann. Int. Med. **10**:1582, 1937.

ARTERIOSCLEROSIS

The question of the relationship of disturbances in cholesterol metabolism to the etiology of arteriosclerosis is still debatable. Leary [38] considers as inadequate the evidence against cholesterol as the essential etiologic agent and believes that the disease of atherosclerosis is due directly to disturbances in cholesterol metabolism. Points of stress in the walls of the vessels determine the localization of the lesions. Apparently any mechanical factor which may interfere with the local nutrition of the vascular wall provides a place in which lipoid deposits will appear. The lesions are primarily intimal, and variations in their character are determined by the age of the patient and by the duration of the lesions. In youth cholesterol gains entrance into the subendothelial tissues, where it is engulfed by lipophages. Young fibroblastic tissue is produced, and these cells engulf the lipoid. This leads to its disappearance from the lesions. Repair with only a small amount of scarring follows. In middle-aged persons the process is similar, but the metabolic processes are slower. Collagen is formed, and scar tissue results. There is nutritional impairment in the scar tissue, and the deeper layers undergo necrosis. Scars are the typical lesions in this period. In old age cholesterol metabolism ceases entirely. The lipophages accumulate in masses, with inadequate nutrition and support, resulting in primary atheromatous abscesses. Calcification arises only after necrosis has developed. It is the terminal phase of the disease and marks the sites formerly occupied by living tissue.

Ochsner and Conner [39] review some of the literature on this subject and report a case of lipoidemia which seems to have been on the basis of a distinct anomaly of lipoid metabolism. Marked atherosclerosis involved almost all the visceral arteries. There were no organic changes suggestive of the named lipoid dyscrasias. The patient died of coronary thrombosis. The cholesterol in the blood plasma reached a level of 667 mg. per hundred cubic centimeters. There was moderate hypertension. In addition to thrombosis of the coronary arteries, the splenic artery was almost completely occluded. There was atherosclerosis of the abdominal aorta, with extensive atheromatous formation. There were no significant lipoid deposits in any other part of the body except the vascular system. The authors conclude that it is reasonable to believe that the disturbance in cholesterol metabolism was the primary manifes-

38. Leary, Timothy: Atherosclerosis: Etiology, Arch. Path. **21**:459 (April) 1936; Atherosclerosis: Special Consideration of Aortic Lesions, ibid. **21**:419 (April) 1936.

39. Ochsner, H. C., and Conner, H. M.: Lipemia Accompanied by Atheromatous and Occlusive Vascular Disease: Report of Case and Partial Review of the Literature, Ann. Int. Med. **10**:258, 1936.

tation and that atherosclerosis was secondary. However, the possibility must be considered that the atheromatous changes and the lipoidemia were due to rupture of atheromatous abscesses.

Freyberg [40] conducted experiments with rabbits, feeding them diets high in vegetable protein, and failed to produce atherosclerotic changes. There was no disturbance in the cholesterol values of the blood except with undernutrition. The author believes that his experiments suggest that the atherosclerosis which developed in rabbits fed on diets rich in muscle meat was due to a nonprotein constituent of the diet and not to the protein itself.

Parhon and Ornstein [41] say that arterial hypertension and hypercholesteremia are the two incontestable factors in the development of arteriosclerosis and atheromatosis. They believe that endocrine dysfunction is the basis for the disturbance in lipoid metabolism, particularly thyroid disorders. They feel that it is rational to consider that hypercholesteremia should be treated by the use of thyroid, as the preventive measure for the development of arteriosclerosis. They report 5 cases in which they were able to control the cholesterol level of the blood by the administration of thyroid or thyroxin.

Eberhard [42] found that when alcohol was administered to rabbits together with cholesterol, the blood values for cholesterol rose more rapidly and to higher levels than in those animals which were fed cholesterol alone. Duff [43] conducted experiments which showed that the lipoid deposits occurred in spontaneous medial lesions of the aorta and that in control animals the spontaneous lesions failed to show the deposits. The lipoid is deposited only at points of vascular injury.

Krafka [44] discusses the numerous etiologic theories in regard to arteriosclerosis. He believes that any theory of sclerosis must be universally applicable throughout all periods of life and to all grades of vascular structures, from the aorta to the smallest vessels. He believes that the mechanical factors are of the utmost importance. He has developed a theory of herniation of the intima, with irritational hyperplasia, as the principal cause of the development of arteriosclerotic changes in all classes of vessels. It accounts for the frequency of the disease in hypertension but does not exclude the occurrence of sclerosis under

40. Freyberg, R. H.: Relation of Experimental Atherosclerosis to Diets Rich in Vegetable Protein, Arch. Int. Med. **59**:660 (April) 1937.

41. Parhon, C. I., and Ornstein, I.: Traitement préventif de l'artériosclérose et de l'athérome artériel, Schweiz. med. Wchnschr. **65**:1164 (Dec. 7) 1935.

42. Eberhard, T. P.: Effect of Alcohol on Cholesterol-Induced Atherosclerosis in Rabbits, Arch. Path. **21**:616 (May) 1936.

43. Duff, G. L.: The Nature of Experimental Cholesterol Arteriosclerosis in the Rabbit, Arch. Path. **22**:161 (Aug.) 1936.

44. Krafka, Joseph: The Mechanical Factors in Arteriosclerosis, Arch. Path. **23**:1 (Jan.) 1937.

conditions of low pressure. Interstices occur in the subendothelial fibers, a variable pressure is always present and herniation results. This provides a simple mechanism for the so-called irritational hyperplasia.

Sappington and Cook [45] made a comparison of the changes in the radial artery and those in the coronary and other visceral arteries. They believe that the Mönckeberg type of sclerosis is entirely independent of, and unrelated to the presence or absence of, atherosclerosis except that both conditions are found in persons over 50 years of age. The anatomic condition of the radial artery has no bearing on visceral sclerosis. The lesions were found to be maximal in the coronary arteries and minimal in the radial arteries, with intermediate degrees of changes in the vessels of the brain, spleen and kidneys.

Kampmeier [46] found arteriosclerosis in 41.8 per cent of 239 Negroes less than 40 years of age. These men showed no evidence of nephritis, hypertension or heart disease. Syphilis was present in only 16. Arcus senilis was found in 85 per cent of the patients with peripheral arteriosclerosis under the age of 40, whereas it occurred in a low percentage of the nonsclerotic patients. Kampmeier believes this association to be significant and that the two diseases may be due to the same etiologic factor. He believes that the high incidence of degenerative vascular disease in the Negro race is to be accounted for on the basis of nutritional deficiency. Just what this deficiency may be is uncertain. He raises the question of vitamin deficiency as well as deficiency in protein and minerals. No cholesterol studies were reported in these cases.

Hallock [47] has confirmed previous conclusions that premature arteriosclerosis occurs commonly in young diabetic patients. Why this occurs in many persons and not in all is still obscure. He has determined the presence of vascular degenerative changes in his group by measuring the rate at which the pulse wave is propagated through the arterial tree. Measurements of the transmission of the radial pulse wave are particularly significant in determining the degree of vascular hardening.

THROMBOSIS AND EMBOLISM

Embolism into the peripheral arteries is said to be the least frequent location, and Bull's figures have been quoted in support of this statement.[48] Embolisms into the lungs, kidneys, spleen and brain are much

45. Sappington, S. W., and Cook, H. S.: Radial Artery Change in Comparison with Those of Coronary and Other Arteries, Am. J. M. Sc. **192**:822, 1936.

46. Kampmeier, R. H.: Arteriosclerosis and Arcus Senilis in Young Negro Male, J. Trop. Med. **39**:164 (July 15) 1936.

47. Hallock, Phillip: Arteriosclerosis in Young Diabetics, Am. J. M. Sc. **192**:371, 1936.

48. de Takáts, Géza: Acute Arterial Occlusions of Extremities, Am. J. Surg. **33**:60, 1936.

more frequent. The work of McKechnie and Allen, reported last year, gives a complete description of the symptoms and findings. De Takáts points out that arterial embolism may have premonitory symptoms. Numbness, coldness or tingling may appear days or weeks before the sudden complete vascular occlusion. The symptoms are the result of the release of minute fragments from the central clot, which is about to break loose. Peripheral thrombosis usually is clear in its differentiation from embolism, but occasionally it is impossible to separate the two conditions. It has been observed in patients as a manifestation of sudden occlusion and the first symptom of widespread arterial disease. Acute vessel spasm following trauma may also be mistaken for acute organic occlusion. The same type of reaction may accompany acute thrombosis, phlebitis or lymphangitis and may be mistaken for embolism. Thrombosis may also quickly follow incomplete occlusion resulting from embolism, so that even on surgical exposure it may be difficult to decide whether the condition represents primary embolism or thrombosis. Reflectoric vessel spasms are an important accompaniment of embolism and may be the essential factor in the development of gangrene.

Gutzeit [49] and Nicole [50] have independently discussed the question of gangrene resulting from the acute arterial spasm that may occur coincidently with venous thrombosis. The symptoms may appear suddenly, with the development of moist gangrene associated with edema which is present as the result of the venous thrombosis. Surface temperature is said to be the most reliable factor in differentiating this condition from embolism. In venous thrombosis the peripheral temperature is normal.

Fatherree and Hines [51] report a case of extensive dry gangrene of the digits and skin of the legs associated with thrombocytopenic purpura. This condition followed an acute illness of two weeks' duration. The cause of the vascular occlusion could not be definitely determined. It was suspected that ergotism might be a factor, although infectious and allergic causes could not be entirely eliminated.

Bargen and Barker [52] report on a group of patients in whom more or less extensive gangrene resulted from multiple arterial and venous thromboses complicating chronic ulcerative colitis. These patients all

49. Gutzeit, R.: Brand durch Venensperre, München. med. Wchnschr. **83**:1628, 1936.

50. Nicole, R.: Arteriospasmus bei akuter Venenthrombose, Schweiz. med. Wchnschr. **65**:676 (July 27) 1935.

51. Fatherree, Thomas J., and Hines, Edgar A., Jr.: Symmetrical Gangrene of the Extremities Associated with Purpura, Am. Heart J. **12**:235, 1936.

52. Bargen, J. Arnold, and Barker, Nelson W.: Extensive Arterial and Venous Thrombosis Complicating Chronic Ulcerative Colitis, Arch. Int. Med. **58**: 17 (July) 1936.

showed exceedingly severe types of the disease. The location of the involvement was chiefly in the large venous trunks, and the extent of the pathologic involvement seemed to be out of proportion to any changes which could be seen in the vascular walls. The inflammatory reactions seen in the pathologic sections seemed to be minimal. It is probable that the essential cause of the thrombosis was the combination of local infection, general toxemia, alterations in the blood and venous stasis. Three of the 6 patients in whom thrombosis occurred died.

Coakley and Klein [53] report a rare condition under the title of progressive postoperative gangrene of the skin. They review the literature on the subject and describe an apparently typical case following appendectomy in which there was extensive gangrene of the skin involving almost the entire abdominal wall. They consider this a clinical entity, although the cause is uncertain. In this particular case the onset was marked by the appearance of a boil. Later this lesion assumed the characteristics of a carbuncle, and finally a spreading infection of the skin developed which rapidly became gangrenous. Culture of material from the wound showed a profuse growth of nonhemolytic streptococci.

THE RAYNAUD SYNDROME

In the past few years the conception of the Raynaud phenomenon as a distinct clinical entity has gradually lost ground. This phenomenon has been recorded in such a variety of clinical states and success has been reported with such a variety of different types of treatment that the condition is much more often part of a syndrome than a distinct disease entity. It is true that in certain cases there is no evident associated or coincidental disease. The etiology is no nearer solution, and whether the fault lies in the peripheral vessels or in the central nervous system is still an open question. However, as was stated in a previous review of this subject, it appears that the fault or sensitized tissue may lie anywhere along the vasomotor tract from the central nervous system to and including the peripheral vessels. It seems relatively unimportant, since the end-result is the same, whether one considers that the fault lies in vessels which are oversensitive to normal stimuli or in an overactive sympathetic nervous system which produces excessive stimulation to the peripheral vessels. The effect of sympathectomy in either case would have essentially the same bearing. Some of these ideas are expressed in an admirable paper on the Raynaud phenomena by John H. Hunt.[54] He critically reviews the subject, including the cases reported by Raynaud.

53. Coakley, Walter A., and Klein, D.: Progressive Postoperative Gangrene of Skin, Am. J. Surg. **33**:287, 1936.

54. Hunt, J. H.: The Raynaud Phenomena: A Critical Review, Quart. J. Med. **5**:399, 1936.

Hunt believes that the term Raynaud's disease would be better changed to the Raynaud phenomenon. He feels that Raynaud's disease is exceedingly rare and that the Raynaud phenomenon occurs in a wide variety of definite and indefinite disorders. He classifies Raynaud phenomena as follows:

A. When the Raynaud phenomenon occurs alone

1. In normal persons exposed to cold long enough to lower the temperature of the blood
2. Hereditary cold fingers
3. Idiopathic Raynaud's disease.
4. After the use of vibrating tools and after local injury to the hands or feet

B. When the Raynaud phenomenon precedes, perhaps by several years, a condition of permanent coldness and cyanosis of the extremities

5. Sclerodactylia

C. When the Raynaud phenomenon is a temporary and often insignificant phase in the development of gross vascular disease of the extremities

6. Thrombo-angiitis obliterans
7. Arteriosclerosis
8. Syphilitic arteritis
9. Rheumatic arteritis
10. Cervical rib
11. In certain cases of pulmonary tuberculosis, leukemia, polycythaemia vera, lupus erythematosus, malaria, chronic arsenical poisoning and many others

This is an ill defined group in need of further subdivision. Hunt points out that as many as seven of these different conditions appear in the original Raynaud thesis.

By experimentation on himself Hunt was able to induce reactions which he believes satisfied all the requirements of the Rayanud phenomenon in a normal person. This was done by lowering the temperature of the blood to points below 35.5 C. As long as the blood or rectal temperature remained above this level the phenomenon could not be induced. The peripheral vasoconstriction which occurs when the body temperature falls several degrees is probably a protective mechanism which prevents too great a reduction in temperature. There is a type of mild vasomotor reaction occurring apparently in normal persons who manifest this sensitivity by blanching or numbness of one or two fingers when exposed to cold. Hunt classifies this as hereditary cold fingers. He calls it the simplest and commonest type of Raynaud phenomenon. Both sexes are affected, and usually other members of the family suffer from vascular disorders or have had chilblains. The author differs from other writers who believe that this type of reaction is a mild manifesta-

tion of Raynaud's disease. The onset usually occurs in childhood, often at about the eighth year. The three points which differentiate this condition from idiopathic Raynaud's disease are sex, family history and age at onset. The attacks vary from slight pallor to cyanosis and numbness of all the fingers of both hands. When the hands are warmed the fingers quickly recover their normal color. This disorder is not progressive; the condition often improves and may even disappear in adult life. It does not lead to any serious trouble or interfere with work. The treatment is essentially the avoidance of exposure of the hands to cold.

In discussing the third group Hunt states that Raynaud's disease is exceedingly rare. Only 1 patient in Raynaud's series can be included under this heading, and Hunt has been able to pick out only about 30 cases from the 500 reported in the English and American literature since the publication of Raynaud's original thesis. The average age at onset of symptoms is apparently 30; females are affected almost exclusively. The clinical picture which he regards as typical is the same as that defined by Allen and Brown. The conclusions of Hunt as to the effects of cooling, overcooling and emotion are essentially the same as those of Lewis. Hunt's description of the changes in color and temperature are also essentially similar to those of Lewis. Between the attacks the hands are usually normal. Nutritional changes, such as superficial sores on the finger-tips, deformities of the nails and the like, are all rare. The nervous system is normal, but many of the patients seem to be of a neurotic disposition. Without treatment the condition in most of these patients becomes steadily worse. Few improve under medical treatment, and he believes that sympathetic ganglionectomy helps all of these patients.

In discussing the fourth group Hunt states that the use of one of the many types of vibrating tools may cause the development of the Raynaud phenomenon. From the nature of the work it is chiefly men who suffer. The author's description is the same as that commonly given in this condition. Nutritional changes in the fingers are rare. The feet are normal, and the hand or hands which hold the tool are usually affected first. General examination usually shows entirely normal findings. When the patient gives up this work, the attacks of cyanosis diminish. He classifies under the same heading those patients in whom vasomotor reactions to cold develop after some local injury to a digit or part of the hand or foot. He states that in both of these types a local fault in the digital or palmar arteries due directly or indirectly to the trauma is an inviting explanation, but the exact cause is not clear.

Under the heading of sclerodactylia Hunt includes many of the conditions which are usually described as Raynaud's disease. This is to be sharply differentiated. He quotes Sellei as saying that sclerodactylia occurs in two different conditions: In the first type the face, hands and

feet may be involved. The disorder usually begins with the skin of the finger-tips and spreads slowly upward, rarely reaching as far as the palm or the dorsum of the hand. The second type is the diffuse or true scleroderma, in which the process begins on the trunk and limbs and spreads distally down the arms so that the dorsum of the hand is involved before the fingers. Females are affected more often than males. When the Raynaud phenomenon occurs in this condition, cold is usually the precipitating factor for an attack, but emotion may sometimes bring it on. The character of the paroxysm is essentially the same as that of Raynaud's disease. Pain is often severe. In the early stages the thickening of the skin may be difficult to recognize, and the fingers may sometimes swell, only to shrink later in the course of the disease. Nutritional changes in the fingers are an important characteristic in this group. Small sores of the finger-tips and superficial gangrene without suppuration are characteristic. Small depressed scars occur which are sometimes tender. Deformities of the nails, shortening of the distal phalanges and whitlows are common. Scleroderma of the face is found to accompany sclerodactylia in about three fourths of the patients. In many of the patients the condition becomes steadily worse. In some it remains stationary and in a few patients attacks of asphyxia occur. In the patients with progressive involvement the hands become more and more fixed and crippled, and the attacks of cyanosis are of longer duration and more severe. In the end the extremities are permanently cold and blue, and the condition no longer satisfies the criteria of the Raynaud phenomena. While many authors have described the relationship between the Raynaud phenomenon and scleroderma or sclerodactylia, many cases of this disorder continue to be reported as Raynaud's disease. Hunt believes that in this condition the local fault will be identified in a microscopic study of the pathologic features of sclerodactylia. In the walls of the arterioles there is intimal thickening, with atrophy and fibrosis of the media and fibrosis around the vessels as well as cellular infiltration in the corium. There is dense fibrosis, with atrophy of the papillae, hair follicles and sweat glands.

The occurrence of vasomotor symptoms begins in the early stages in about a third of the patients with thrombo-angiitis obliterans. Symptoms of this type, with intermittent pallor or cyanosis, may last for several months before the onset of claudication or rest pain. As the disease advances, these vasomotor phenomena of the Raynaud type disappear. Similar conditions occur in arteriosclerosis, and Hunt believes that attacks of cyanosis may frequently be found in arteriosclerosis.

The typical Raynaud paroxysm has been associated with both congenital and acquired syphilis. It is a working rule with Hunt to suspect the presence of syphilitic endarteritis whenever the Raynaud phenomena are associated with necrosis of the ears or nose or with hemoglobinuria.

The paroxysm in cases of this type probably results from local vascular injury. With antisyphilitic treatment the results are often excellent, and this no doubt accounts for the reports of the cure of Raynaud's disease with antisyphilitic treatment.

In rheumatic arteritis much the same series of events may take place. Typical Raynaud phenomena may occur, associated with rheumatic conditions following streptococcic infections. They usually subside when improvement begins.

In Hunt's opinion, most of the cases of cervical rib which have been reported do not fulfil the requirements for the Raynaud phenomenon. There are usually continuous and not intermittent vascular spasms.

On the last group, which appears to be an important one, Hunt is able to throw little light. In all these conditions typical Raynaud phenomena are occasionally seen. Why they occur is unknown. It is in this group that many new cases reported as Raynaud's disease belong. In addition to the diseases mentioned by Hunt, the group of endocrine disorders with Raynaud phenomena, arthritis and diseases of the central nervous system as well as arsenic intoxication may be placed.

Prinzmetal [55] reports on some interesting studies on what he calls the mechanism of circulatory insufficiency in Raynaud's disease in association with sclerodactylia. Contrary to Hunt, it is his opinion apparently that sclerodactylia is superimposed on Raynaud's disease, and when this occurs the ischemic process becomes gradually intensified, and gangrene occurs. In the form of the Raynaud syndrome associated with sclerodactylia the clinical symptoms, according to this author, are severe, and the vascular reactions differ from those of the typical Raynaud syndrome in that there are superimposed the mechanical effects of the changes in the skin which result in a constricting band which mechanically interferes with the flow of blood through the vessels of the fingers. This ischemia affects not only the larger vessels but the arterioles, capillaries and veins, and it is the capillary constriction particularly which probably is largely responsible for the impairment of nutrition in the tissues. Prinzmetal ingeniously devised a method by which the normal finger could be made to simulate and produce vascular reactions identical with those of actual sclerodactylia.

Sunder-Plassmann and Mueller [56] report on a patient with so-called Raynaud's disease in whom there were disturbances in both carbohydrate and calcium metabolism. They were able to control the paroxysm by injecting an anesthetic into the stellate ganglion and

55. Prinzmetal, Myron: Studies of the Mechanism of Circulatory Insufficiency in Raynaud's Disease in Association with Sclerodactylia, Arch. Int. Med. **58**:309 (Aug.) 1936.

56. Sunder-Plassmann, P., and Mueller, K.: Morbus Raynaud und neurovegetative-hormonales System, Klin. Wchnschr. **16**:162 (Jan. 30) 1937.

effecting bilateral removal of this structure. This was followed by a return to normal of both carbohydrate and calcium levels in the blood. They express the opinion that Raynaud's disease represents a disturbance of the entire autonomic nervous system, central as well as peripheral, and that the hormones associated with the neurovegetative system are equally disturbed. This case suggests the ones which have been reported by Garlock,[57] in which marked improvement occurred either after calcium management or after parathyroidectomy. Garlock states that most patients suffering from Raynaud's disease sooner or later show changes in the skin which come under the classification of scleroderma, and this is usually evident in the fingers and hands. He feels that the development of scleroderma is preceded by vasospasm of the same type as that which occurs in Raynaud's disease. This of course is in contrast to the definite ideas expressed by Hunt, who feels that the Raynaud phenomenon is part of the course of scleroderma. Garlock's views, as expressed in his recent publications, are essentially the same as those reported in the review of last year.

Linenthal[58] reports a case of Raynaud's disease with pulmonary complications, which is apparently one of scleroderma. Numerous instances of visceral fibrosis have been reported in association with scleroderma.

As another example of Hunt's group 2 is the case reported by Klinefelter[59] regarding the successful treatment of Raynaud's disease with estrogenic substance. This was obviously an example of Raynaud syndrome occurring in a patient with endocrine dysfunction, with symptoms of menstrual disorder with hot flashes. The Raynaud paroxysms disappeared when the menstrual cycle returned to normal.

Rechtman[60] adds 2 cases to the few which have been reported in males. These cases appeared to fulfil the requirements for the diagnosis of idiopathic Raynaud's disease.

Smithwick[61] also reports cases in which scleroderma eventually developed after years in which the Raynaud syndrome was a prominent complaint. He also comments on extensive pulmonary fibrosis, with diminished vital capacity and excessive perspiration of the involved extremities in this group.

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57. Garlock, J. H.: Parathyroidectomy for Raynaud's Disease and Scleroderma, S. Clin. North America **16**:771, 1936.

58. Linenthal, H.: Pulmonary Complications in Raynaud's Disease, New England J. Med. **216**:188 (Jan. 28) 1937.

59. Klinefelter, Edmund W.: Successful Treatment of Raynaud's Disease with Estrogenic Substance, Arch. Dermat. & Syph. **34**:887 (Nov.) 1936.

60. Rechtman, A. M.: Raynaud's Disease in Man, Ann. Int. Med. **10**:549, 1936.

61. Smithwick, R. H.: The Value of Sympathectomy in the Treatment of Vascular Disease, New England J. Med. **216**:141 (Jan. 28) 1937.

Adson [62] includes under the heading of Raynaud's disease the typical phenomenon of vasospasm, which he says varies in degree from mild discomfort to ulcerative gangrene of the digits, with sclerodactylia and what he calls dactyl arthritis. He repeats the previous arguments on which he bases the assumption that the Raynaud phenomenon is the result of a fault in the central mechanism of the autonomic nervous system.

Vasospastic Disease Due to the Use of Vibrating Tools.—Drenckhahn [63] discusses this type of vasospastic disease and reports a group of cases in which the disorder developed in coal-miners who used picks. He believes that this vasospastic disease which occurs as the result of the use of vibrating tools, particularly in stonecutters and shoemakers, is produced in miners as the result of vibration in a particular type of patented pick. The symptoms which he describes as occurring in these men are identical with those of previous descriptions of this disorder. Hunt [64] makes an additional report of 7 cases of this type of vasospastic disease occurring in riveters in a locomotive workshop. In these men the attacks of syncope occurred in winter only. They increased in severity and finally were present even in warm weather. The symptoms varied from light pallor of the finger-tips to cyanosis of the whole hand. If a finger was cut while in this state, little or no bleeding occurred. When warmth was applied, the fingers rapidly regained their normal color. It is interesting to note that emotion played no part in precipitating these attacks, nor did vibration alone without cold. Another interesting fact noted by Hunt is that symptoms did not occur among the men working with hot rivets. This is probably because there is less vibration induced by the riveting machine when hot rivets are used.

Mikkelsen [65] draws attention to the occurrence of posttraumatic arteriospasm in the fingers. It follows injuries of various types and may involve even the hand. He describes 2 cases following Colles' fracture. He believes that conditions of this type may easily be confused with or mistaken for neuroses. Pain, coldness, pallor and unusual susceptibility to cold are important symptoms. Protecting the fingers from cold, splinting and bandaging are often effective forms of treatment.

62. Adson, Alfred W.: Physiologic Effects Produced by Ablation of the Autonomic Central Influence: Various Forms of Sympathectomy in the Treatment of Diseases, Surgery **1**:425, 1937.

63. Drenckhahn, C. H.: Vasospastic Disease of the Hands of Miners Due to Vibration, Illinois M. J. **70**:354, 1936.

64. Hunt, J. H.: Raynaud's Phenomenon in Workmen Using Vibrating Instruments, Proc. Roy. Soc. Med. **30**:171, 1936.

65. Mikkelsen, O.: Posttraumatiske arteriospasmer paa fingrene, Hospitalstid. **80**:177 (Feb. 16) 1937.

PRIMARY IDIOPATHIC THROMBOPHLEBITIS

It is under this term that Barker [66] presents a careful study of the condition which has usually been recorded under the term thrombophlebitis migrans. The report covers a group of 79 patients in whom none of the known causes of thrombophlebitis and conditions which it sometimes complicates were present. There were no recognizable factors of abnormal venous stasis. He divides the patients into two groups: In one group the condition was recurrent and of the type of thrombophlebitis migrans, and in the other group there was no repetition of the episode. The disease was not limited by age or race, although the majority of patients were men. The frequency of recurrence was variable. The veins of both legs were involved in the majority of patients, although lesions appeared in both arms and in both legs. The lesions of the superficial and saphenous veins appeared to be inflammatory in all the patients and could be felt as firm indurated cords which were tender and showed surrounding inflammatory reaction. Fever was variable, pulmonary embolism was not uncommon and edema occurred in many of the patients. Special studies of the blood failed to reveal anything of significance, and culture of material from the thrombosed veins remained sterile. The group in which there was only a single episode presented much the same characteristics during the illness as did the group with recurrent episodes.

Although Barker recognizes the relationship of this disorder to thrombo-angiitis obliterans, he feels that there are definite differences in the venous involvement. The entire absence of involvement of the arteries is important. The limitation as to age and sex is not so certain. Large veins are frequently involved. Pathologically there is less proliferation of connective tissue than in thrombo-angiitis obliterans. The author feels that this is a definite clinical entity and that as yet no etiologic factor can be named.

Tomasi [67] reports a case of axillary thrombophlebitis with the pathologic observations made after amputation for gangrene. The arteries appeared to be normal. All the veins were involved, with massive occlusion of the venous system of the arm. This represents a case of gangrene of purely venous origin. Infection was an essential factor.

SECONDARY THROMBOPHLEBITIS

In inflammatory conditions involving the veins, with thrombosis, or thrombosis occurring as the result of alterations in the blood or after

66. Barker, Nelson W.: Primary Idiopathic Thrombophlebitis, Arch. Int. Med. **58**:147 (July) 1936.

67. Tomasi, L.: A Contribution to the Pathology and Clinical Features of Thrombophlebitis of the Upper Extremities, Arch. ital. di chir. **43**:525, 1936.

stasis, the phenomena are so varied and so well known that little can be said of them here. It is, however, interesting to note that Altschüler [68] reports on 2 patients with tuberculous thrombophlebitis of the lower extremities in whom there was no adjacent tuberculous disease. Only the intima was attacked. The inguinal glands were removed and examined, and no evidence of tuberculosis was obtained. This was apparently the only site of the tuberculous process in either patient. The author thinks that this type of involvement may not be as uncommon as now appears.

POLYCYTHAEMIA VERA AS A VASCULAR DISEASE

Norman and Allen [69] discussed polycythaemia vera from the standpoint of its vascular complications and report on a group of 98 patients. Vascular phenomena occurred in a large proportion of this group. In addition to myocardial infarction, angina pectoris, cerebral hemorrhage or thrombosis, intra-abdominal thrombosis, occlusive disease of the peripheral arteries and vasomotor neuroses occurred. The authors point out that this disease often occurs at the time of life when degenerative vascular disease is common and that thrombosis of both arteries and veins occurs in a much larger proportion of the patients than could ordinarily be expected. The actual incidence of degenerative vascular disease is also high. In some instances chronic occlusive arterial disease occurred which could not be distinguished from arteriosclerosis obliterans. The authors comment on the frequency of burning paresthesia simulating erythromelalgia. One patient presented symptoms suggesting the Raynaud syndrome. Vascular lesions also occurred with relative polycythemia, including such conditions as thrombo-angiitis obliterans as well as arteriosclerosis. The authors believe that treatment of polycythaemia vera is important in order to prevent vascular complications.

ERYTHROMELALGIA

Mufson [70] agrees that erythromelalgia is a symptom complex dependent on minute vascular changes of unknown etiology. He made a careful study of 2 patients who exhibited this syndrome. Capillary studies and observations on capillary and venous pressures showed an exaggerated reaction to warmth, with dilatation and an increase of pressure in these vessels. He feels that this dilatation is the result of the absence of normal antagonistic vasoconstriction and that symptoms could be relieved for as long as a few days by the intravenous

68. Altschüler, E.: Tuberculous Thrombophlebitis of the Lower Extremity, Lancet **1**:948 (April 25) 1936.

69. Norman, I. L., and Allen, E. V.: The Vascular Complications of Polycythemia, Am. Heart J. **13**:257, 1937.

70. Mufson, Isidor: Clinical Observations in Erythromelalgia and a Method for Its Symptomatic Relief, Am. Heart J. **13**:483, 1937.

infusion of epinephrine hydrochloride and even by the inhalation of a 1:100 solution. In 1 patient it seemed as if chronic alcoholism might have been a factor. The dilatation and increase in capillary pressure occurred coincidently with the development of pain.

TREATMENT

That the treatment of peripheral vascular diseases has been well stabilized is shown by the large number of papers on this subject. Most of these recount experiences with methods that are well established and are largely reviews or summaries the subjects of which have been considered in previous reviews in this journal.

Subsequent reports [48] express satisfaction with the use of papaverine hydrochloride as a valuable aid in the management of cases of sudden arterial occlusion. This drug should be used in conjunction with other aids, including heat properly applied and of the right degree, together with negative pressure in overcoming the associated vessel spasm.

Berens [71] reports most gratifying results in the treatment of thromboangiitis obliterans with sodium thiosulfate and sodium iodide according to the ideas of Rabinowitz. The basis for this treatment was reviewed last year. The favorable results following the arterial injection of iodine-containing contrast mediums have been reported in the European literature. Beutel and Klein [72] have given as many as thirteen injections to 1 patient. They believe that in some cases this injection treatment will postpone or prevent the amputation of an extremity when all other methods have failed. They state that the patient experiences a burning sensation which is accompanied with dilatation of the surface capillaries, as shown by capillaroscopy.

Ratschow [13] regards the injection of neo-iopax or abrodial (the sodium salt of mono-iodomethane sulfonic acid) intra-arterially into patients with severe vascular disease as a method so efficacious that it cannot be ignored. He quotes previous workers on the subject and feels that in all cases of severe gangrene this method should be employed before amputation is performed. There have been no reports of the use of substances of this type in the American literature.

Ewald,[73] in discussing the therapy of embolism, points out the difficulties in the recognition of latent deep venous thrombosis. This dis-

71. Berens, S. N.: Use of Sodium Thiosulphate and Sodium Iodide in Case of Buerger's Disease (Thrombo-Angiitis Obliterans), J. Chemotherapy **13**:106, 1936.

72. Beutel, A., and Klein, O.: Percutaneous Arteriography as a Therapeutic Method, Med. Klin. **32**:899 (July 3) 1936.

73. Ewald, C.: Therapy of Thrombophlebitis and of Thrombo-Embolism, Wien. med. Wchnschr. **86**:537 (May 16) 1936.

order may appear with or without signs of inflammation. In order to prevent the detachment of the thrombus he emphasizes the importance of complete rest and proper position of the limb. The lower part of the leg should be supported so that the knees are bent, and elastic bandages should be carefully applied in order to prevent the release of a portion of the thrombus.

An interesting development in the mechanical treatment of vascular diseases is that reported by Collens and Wilensky.[74] They have employed the principles of reactive hyperemia by the application of intermittent venous occlusion. They claim that this is in no way related to intermittent suction and pressure. Their procedure is based on the principle of reactive hyperemia. A pneumatic cuff is applied about the proximal portion of the extremity, and a pressure of from 60 to 80 mm. of mercury is applied in alternating periods of two minutes each. They report on the treatment of a group of 29 patients for whom no other treatment was used except rest in bed. The most outstanding results which they obtained were the complete and rapid relief from pain. Ulcers showed an unusual tendency to heal. They report on 1 patient with thrombo-angiitis obliterans who had been under treatment by generally accepted methods for seven years without relief from pain or any influence on the state of the ulcer. At the end of twelve hours of treatment by intermittent venous compression there was some relief from pain. Within five days the patient was able to sleep without the use of a narcotic or sedative for the first time in many months. In eight weeks the ulcer completely healed. No mention is made of previous treatment by alternating suction and pressure. The authors report the relief from pain in less than twenty-four hours in all the five other patients with thrombo-angiitis obliterans. In 23 patients with arteriosclerosis obliterans, 13 of whom were diabetic, complete relief from pain was obtained in 17, partial relief in 5 and none in 2. When relief occurred it was apparent in from two to forty-eight hours of treatment. The authors believe that gangrene of 2 patients with diabetes was made definitely worse by this treatment, and the necessity for amputation was hastened. In 4 other patients healing occurred, and 5 more showed healing at the time of the report. Patients with intermittent claudication were uniformly relieved. In the patients with ulcer or gangrene they were able to obtain the greatest amount of relief by maintaining a pressure of from 40 to 50 mm. of mercury for periods of one hour alternating with one hour of rest. This is indeed an encouraging report, and the method deserves careful follow up.

74. Collens, William S., and Wilensky, Nathan D.: The Treatment of Peripheral Obliterative Arterial Diseases, J. A. M. A. **107**:1960 (Dec. 12) 1936.

The value and limitation of the use of alternating suction and pressure have apparently been well established. Relatively little change has been offered in regard to these factors. Almost all reports are encouraging, and it seems that this method is well established in its field of usefulness. The limitations have been discussed in previous reviews. Bierman [75] considers that the compression made around the leg by the cuff which is used to seal off the device in which the leg is placed is an essential defect. No matter how arranged, the cuff causes some embarrassment to venous circulation and to a lesser degree to the arterial circulation. Barker [76] is apparently not at all certain as to the general value of this method of treatment. He suggests that it has its place, particularly in the treatment of rest pain, acute arterial occlusion, frost-bite and mild ischemia.

Edwards [77] has devised a chamber for applying the proper degree of heat to the extremity in order that the proper local effect of warmth on the arterioles and smaller vessels may be obtained, as has been emphasized by Herrmann. He points out that locally applied warmth is capable of producing maximum vasodilatation and increases the effectiveness of suction. The local increase in metabolism caused by the raised temperature assists the process of healing.

Board [78] reports favorable results with the method. In his experience the most striking benefits have been obtained following the ligation of a large artery or sudden occlusion of the vessel. Frozen feet responded promptly if intensive treatment was begun before complete obliteration of the arterioles had taken place. He also has been disappointed in the treatment of thrombo-angiitis obliterans.

Bloom and Porter [79] have been encouraged by their results. Patients suitable for suction and pressure treatment should be carefully selected and adequately supervised while under treatment.

Interesting observations on changes in the oxygen content of the blood after passive vascular exercise are reported by Veal and McCord.[80] By means of these determinations they feel that the prognosis in some

75. Bierman, W.: Diagnosis and Treatment of Peripheral Vascular Disease by Physical Agents, New York State J. Med. **36**:1405 (Oct. 1) 1936.

76. Barker, Nelson W.: Physical Agent in Treatment of Circulatory Diseases of Extremities, Arch. Phys. Therapy **17**:554, 1936.

77. Edwards, E. A.: Treatment of Organic Arterial Obstruction by Alternating Suction and Pressure, J. A. M. A. **108**:626 (Feb. 20) 1937.

78. Board, O. P.: Passive Vascular Exercises in Treatment of Obliterative Vascular Disease, South. Surgeon **5**:255, 1936.

79. Bloom, Nathan, and Porter, William B.: Problems in the Diagnosis and Treatment of Peripheral Vascular Disease, Virginia M. Monthly **64**:7, 1937.

80. Veal, J. Ross, and McCord, William M.: Blood Oxygen Changes After Passive Vascular Exercise of the Extremities, Proc. Soc. Exper. Biol. & Med. **36**:9, 1937.

cases can be predicted. An increase in oxygen saturation of either the superficial or the deep venous blood or both after one hour's trial indicates that some improvement will follow this form of therapy. When there is no change or fall in oxygen saturation the prognosis is poor. They note a wide discrepancy between the changes in the oxygen content of blood from deep and that from superficial vessels after treatment with suction pressure.

Theis and Freeland [81] have also made extensive studies on the effect of treatment with alternating positive and negative pressure on the temperature of the venous blood of the skin. The temperature of the skin was taken under controlled conditions before and after each period of treatment. Analyses of the venous blood of the extremities for oxygen and carbon dioxide were made before and one hour after treatment with suction and pressure to both lower extremities and after heat at 45 C. had been applied to the upper extremities for direct and indirect effects. In addition the authors made tests of the body metabolism and the oxygen consumption per minute before and one hour after treatment with alternating positive and negative pressure to both lower extremities and with heat applied to both upper extremities to increase the circulation of blood. They state that in their experience this procedure is the most effective means of relieving the pathologic changes which take place in the tissue owing to deficient circulation. They believe that the beneficial effects of this method of treatment are on the physiologic basis of increased tissue metabolism. The heat produces an increased blood flow, and the pressure treatment increases the exchange of oxygen and carbon dioxide in the tissues. Ordinarily no estimate can be made of the permanent effect of treatment by analyses of the exchange of oxygen and carbon dioxide in the tissues. Readings of the peripheral temperature are of value in determining how frequently and how intensively the treatment should be given. The authors think that the respiratory function of the skin may be an important factor in the success of pressure treatment. Keeping the skin soft and pliable probably aids in the absorption of oxygen from the air and the elimination of carbon dioxide. The oxidation process which is increased during treatment with positive and negative pressure may account for the increased temperature of the skin. Vasodilation as the result of direct or reflex heat is more effective in increasing peripheral circulation, but apparently it has little effect in increasing metabolism in the tissues and only increases the available supply of oxygen, The combination of these methods is of greater clinical value than is either method alone.

81. Theis, Frank V., and Freeland, M. R.: Peripheral Circulatory Diseases, J. A. M. A. **107**:1097 (Oct. 3) 1936.

A CRITICAL REVIEW OF THE LITERATURE ON SURGICAL TREATMENT

By Dr. de Takáts

Contributions published since my last review can again be grouped as dealing with (1) attempts to improve the circulation, (2) attempts to relieve pain and (3) methods of amputation.[82]

REMOVAL OF VENOUS THROMBI

Läwen [83] reports on 3 patients from each of whom a venous thrombus was extracted shortly after its formation (one subclavian thrombus and two iliofemoral thrombi). Not only does the concomitant arterial spasm disappear, but the venous return is markedly improved. Further observation will be necessary to establish the indications, the optimal time for this procedure and the possible hazards of pulmonary embolism. Vascular and nutritional disturbances following venous thrombosis in certain patients have been relieved by stripping the vein from the surrounding exudate or scar tissue, which is a simpler procedure.[84]

ARTERIECTOMY

Leriche and his co-workers [85] have republished their work on arterial excision in patients suffering from organic arterial occlusion, which was previously reviewed. Relief from symptoms was obtained in 43.6 per cent of the patients. The authors state that the operation is not as satisfactory as lumbar sympathectomy, but it involves much less risk. Leriche emphasizes again that an obliterated artery ceases to function as a carrier of blood and becomes a diseased plexus of sympathetic nerve fibers which maintain vascular spasm. While this is an important and fruitful principle and deserves consideration in all types of arterial obstruction, his results with arteriectomy are not encouraging. In the occasional case of traumatic or infectious thrombosis or instead of simple arterial ligature, arteriectomy may prove to be of great value.

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82. No attempt has been made to offer a complete bibliography. Articles have been selected which contain new trends of thought or which crystallize previously suggested ideas.

83. Läwen, A.: Ueber Thrombektomie bei Venenthrombose und Arteriospasmus, Zentralbl. f. Chir. **64**:961 (April 24) 1937.

84. de Takáts, G.: Reflex Dystrophy of the Extremities, Arch. Surg. **34**:939 (May) 1937.

85. Leriche, R.; Fontaine, R., and Dupertuis, S. M.: Arteriectomy, with Follow-Up Studies on Seventy-Eight Operations, Surg., Gynec. & Obst. **64**:149, 1937.

EMBOLECTOMY

A thorough and instructive report on the late results of embolectomy is given by Hindmarsch and Sandberg;[86] 77 per cent of the patients suffered from chronic heart disease, and 6 per cent had undergone an operation or childbirth. When embolectomy was performed within the first ten hours after the onset of symptoms, 58 per cent regained normal circulation; 35.7 per cent of those operated on after the elapse of more than ten hours obtained a good functional result. All axillary and brachial embolectomies were successful. Two thirds of the patients whose extremities were saved died within ten years, the condition of the heart determining the outcome.

Pain, the early symptom of arterial embolism, is analyzed by Sir Thomas Lewis.[87] In embolism of an artery of a limb, pain and tenderness may occur at the site of the clot as a late symptom, but the early pain is not due to the impact of the clot, it is due to ischemia distal to the obstruction, chiefly in the muscles of the limb. Thus, embolism or thrombosis gives rise to pain when it affects muscular organs, like the limb, the heart or the bowel, but not when its effects are confined to nonmuscular organs, like the brain, the lung or the spleen.

In a lecture on embolism of an artery Nystrom[88] summarizes his vast personal experience and that of the group of Swedish surgeons concerning the early diagnosis and treatment of peripheral arterial embolism. He strongly believes in the early exposure of the occluded artery and offers a number of helpful technical suggestions. Half of his 32 patients operated on within the first ten hours were discharged with a restored circulation. Less favorable were the data on results collected from reports of 382 cases, the total Swedish material. The late results were as follows: Twenty per cent of the patients were discharged with a restored circulation, 20 per cent were discharged after amputation and 60 per cent died. In this country those who are interested in vascular surgery seldom see a patient for whom embolectomy is suitable, as the favorable time for operation is frequently missed. It is encouraging to note, however, that in a recent paper from the Cincinnati General Hospital, Herrmann[89] could report on 53

86. Hindmarsch, J., and Sandberg, I.: Forty-Five Embolectomies, Acta chir. Scandinav. **78**:81, 1936.

87. Lewis, T.: Pain as an Early Symptom of Arterial Embolism and Its Causation, Clin. Sc. **2**:237, 1936.

88. Nystrom, G.: Lectures on Embolism and Other Surgical Subjects, Baltimore, Williams & Wilkins Company, 1936.

89. Herrmann, L. G.: Experiences with the Conservative Management of Acute Arterial Occlusion, read at the Thirteenth Annual Meeting of the American Heart Association, Atlantic City, June 7, 1937.

patients with acute arterial occlusion, roughly half of whom arrived at the hospital within twelve hours. With a combination of heat, vasodilation and suction and pressure therapy the extremity was saved in more than half the cases. This result is better than any other reported after embolectomy. The next few years will show whether the limbs saved by conservative measures will be as useful and painless as the ones in which embolectomy has reestablished the major arterial pathways. The time factor is so important that further education of the general medical profession seems indicated.

Increasing interest in the influence of climatic conditions on vascular accidents is reflected in a number of articles. A review of these with a number of clinical correlations is presented in Petersen's monographs on the patient and the weather. In his recent volume on cardiovascular and renal disease he [90] again emphasizes the significance of pressor episodes and the associated rôle of anoxia brought about by meteorologic conditions. As Bärtschi [91] states, the present evidence does not allow one to postulate that an operation should be carried out only in "anticyclonic" weather, but if confirmed on a larger material it may point in that direction. Certain it is that every one dealing with data on arterial and venous thromboses must be impressed with certain seasonal and climatic influences. These observations, however, will obtain clinical significance only if simple practical methods of avoiding or buffering these pressor episodes can be worked out.

ARTERIOVENOUS ANEURYSM

The replacement of a long arterial segment with a venous transplant has been reported in 2 cases.[92] In each patient a large traumatic aneurysm necessitated an extensive loss of a major arterial trunk, which was successfully replaced by a transplant of a long segment from the long saphenous vein. This is a principle which has been promulgated from time to time, but few permanent end-results have been reported. Plugging of an aneurysmal sac with a pedicled muscle flap and repair of an arterial wound with a muscle flap rolled around the vessel have been experimentally and clinically studied by McNealy and Shapiro,[93] and the results seem most encouraging.

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90. Petersen, W. F.: The Patient and the Weather: I. Cardio-Vascular-Renal Disease, Ann Arbor, Mich., Edwards Brothers, Inc., 1937, vol. 4.

91. Bärtschi, W.: Embolie und Wetter, Schweiz. med. Wchnschr. **66**:1209 (Nov. 28) 1936.

92. Karitzky, B.: Gefässverletzungen und ihre Behandlung, Zentralbl. f. Chir. **64**:8 (Jan. 2) 1937.

93. McNealy, R. W., and Shapiro, P. F.: Arterial Repair by Muscle Transplants, Surgery **2**:61, 1937.

A case of traumatic arteriovenous fistula is reported by Dry and Horton [94] in which there was spontaneous closure after twenty-five years. While the affected limb was larger and longer, there was no intermittent claudication. Such a case has not been previously recorded. The Branham sign—bradycardia following pressure over the arteriovenous fistula—is analyzed by Tournade and Curtillet,[95] who give two possible explanations. The sign, which had really been described by Nicoladoni long before Branham made his report, may be due to a depressor reflex mediated through the vagus nerve or to an alternating pulse due to the sudden rise in general blood pressure.

CERVICAL RIB AND THE SYNDROME OF THE SCALENUS ANTICUS MUSCLE

Symptoms similar to those produced by a cervical rib but due to a tight scalenus anticus muscle are discussed by Flothow [96] and by Craig and Knepper.[97] According to Craig and Knepper, the symptoms result from compression or irritation of the brachial plexus and compression of the subclavian artery. Compression may be due to the presence of a cervical rib, an abnormally low position of the shoulder, a high fixation of the sternum and ribs, a low origin of the brachial plexus or elevation of the first rib from spasm of the scalenus muscle, which, in turn, is brought about by irritation of the plexus. Resection of the anterior scalenus muscle is usually all that is necessary, but when there is evident pressure from a cervical rib or its tendinous attachment, resection of the rib or its attachment should be carried out. In my experience these patients have frequently been said to have Buerger's disease, Raynaud's disease or a vegetative neurosis. That many of them are neurotic is more the result than the cause of definite organic findings; but a certain constitutional inferiority may be present.

Lindgren [98] reports on a patient who had an abnormally high and bulbous first thoracic rib which caused circulatory disturbances in the corresponding arm. Section of the anterior scalenus muscle and removal

94. Dry, T. J., and Horton, B. T.: Traumatic Arteriovenous Fistula Involving the Right Femoral Artery and Vein: Spontaneous Closure, Arch. Surg. **33**:248 (Aug.) 1936.

95. Tournade, A., and Curtillet, E.: L'anévrysme artério-veineux expérimental: Note complémentaire sur l'épreuve de Branham, Compt. rend. Soc. de biol. **122**: 15, 1936.

96. Flothow, P. G.: Cervical Rib and Anterior Scalenus Syndrome, West. J. Surg. **44**:570, 1936.

97. Craig, W. M., and Knepper, P. A.: Cervical Rib and Scalenus Anticus Syndrome, Ann. Surg. **105**:556, 1937.

98. Lindgren, S.: Vascular Disease of Upper Extremity with Abnormality of First Thoracic Rib, Acta chir. Scandinav. **79**:81, 1936.

of the anomalous rib did not give relief. It was found that the patient had an aneurysm of the subclavian artery distal to the compression and segmental obliteration of the brachial artery, demonstrated by arteriography. This condition would be suitable for local arterial excision, as advocated by Leriche.[85]

SYMPATHECTOMY

Experimental work on the rôle of the vegetative nervous system on peripheral circulation has continued during the past year. On a large series of dogs Albert and Dumont[99] used arteriography to study the effect of various types of sympathectomy. They found that the removal of the entire lumbar chain with the first sacral ganglion gave the greatest enlargement of the visualized vascular bed. Unfortunately, these were all acute experiments, and no late results are reported.

Bülbring and Burn[100] found in dogs that the vessels in the skin of the hindlimb receive no dilator sympathetic supply but that the muscles do. The dog's ear is different, because after paralysis of the vasoconstrictors with ergotoxine, stimulation of the sympathetic nerve causes dilatation of the aural vessels. Surgeons performing sympathectomies will be reminded by this article that vasodilators are carried in the sympathetic nerves, although obviously the major vasodilator outflow is through the posterior root ganglions. The vasodilator reactions, dependent on intact spinal ganglions, have been studied by Wybauw.[101] When the spinal ganglions were removed from cats and postganglionic degeneration occurred, there resulted no hyperemia after exposure to cold. This reaction is due to an axon reflex regulated by vasodilators the trophic cell of which is in the posterior root ganglion. Section of the posterior root proximal to the ganglion does not abolish this reflex.

The absence of these axon reflexes, previously studied by Sir Thomas Lewis, well explains the formation of "trophic" ulcers in areas devoid of normal sensation. It also indicates that sympathectomy for trophic ulceration is of no avail.

In a significant contribution by Freeman, Shaw and Snyder[102] a report is made of studies of the blood flow through the hand. A reduc-

99. Albert, F., and Dumont, P.: La chirurgie du sympathique lombaire: Etude artériographique expérimentale, Rev. belge sc. méd. **8**:445, 1936.

100. Bülbring, E., and Burn, J. H.: Sympathetic Vaso-Dilatation in Skin and Intestine of Dog, J. Physiol. **87**:254, 1936.

101. Wybauw, L.: Rôle des ganglions rachidiens dans le mécanisme des réactions vasodilatatrices cutanées au froid et au chaud chez le chat, Compt. rend. Soc. de biol. **122**:456, 1936.

102. Freeman, N. E.; Shaw, J. L., and Snyder, J. C.: Peripheral Blood Flow in Surgical Shock: Reduction in Circulation Through Hand Resulting from Pain, Fear, Cold, and Asphyxia, with Quantitative Measurements of Volume Flow of Blood in Clinical Cases of Surgical Shock, J. Clin. Investigation **15**:651 (Nov.) 1936.

tion was found to result from pain, fear, cold and asphyxia. The authors point out that the arterial blood pressure does not necessarily indicate the adequacy of blood flow through the tissues; in fact, the blood pressure may be increased by epinephrine or ephedrine only at the expense of the nutrition of tissues. In the sympathectomized limb there was an increase of blood flow after partial asphyxia, whereas in the normal limb the results were variable. Observations on patients for each of whom one limb had been sympathectomized have shown that a stimulus which normally produces reflectoric vasoconstriction may result in a paradoxic increase of pulsations in the sympathectomized extremity.[103]

By far the most important contribution of the year to the experimental surgery of the sympathetic nerves is that of Ascroft.[104] He studied the early and late effects of the division of the vasomotor fibers in the rhesus monkey. Cutaneous temperatures were used to measure the rate of blood flow. Preganglionic operations were more effective in producing chronic vasodilatation than were postganglionic sections, and it seems rational in all cases to replace postganglionic sympathectomy by preganglionic division. In man all preganglionic fibers may be interrupted to the upper extremity by dividing the thoracic sympathetic chain just below the second ganglion and by severing connections to the second thoracic nerve. Horner's syndrome is thus avoided. On the lower extremity it might be well to leave the fourth lumbar ganglion intact, removing only the second and the third, for no white ramus reaches the fourth ganglion, and it gives off a gray ramus carrying postganglionic vasomotor fibers.

This work reemphasizes and corroborates the disadvantage of sensitizing vessels to various stimuli when postganglionic degeneration occurs. As mentioned in the last two reviews, the work of J. C. White and E. D. Telford points to preganglionic section as the method of choice. Although a certain amount of sensitization develops after this type of procedure, both experimental and clinical evidence indicate that this procedure is preferable. My limited experience is definitely in favor of preganglionic section.[103]

Some evidence is gradually accumulating that even after complete sympathectomy peripheral vasoconstrictor mechanisms exist which maintain vascular tonus and blood pressure. Thus, Wilson, Roome and Grimson [105] studied the blood pressure of completely sympathectomized

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103. de Takáts, G.: The Effect of Sympathectomy on Peripheral Vascular Disease, Surgery **2**:46, 1937.

104. Ascroft, P. B.: The Basis of Treatment of Vasospastic States of the Extremities: An Experimental Analysis in Monkeys, Brit. J. Surg. **24**:787, 1937.

105. Wilson, H.; Roome, N. W., and Grimson, K.: Complete Sympathectomy, Ann. Surg. **103**:498, 1936.

dogs and found that it remained at a higher level than would be expected after the withdrawal of all vasoconstrictor impulses. They suggest the possibility of a peripheral vasoconstrictor mechanism. This is in line with Hirt's [106] view, reemphasized by Starlinger,[107] that beside the main efferent sympathetic pathways there is an accessory pathway through the spinal ganglion from both anterior and posterior roots which does not enter the sympathetic chain. The histologic evidence of a widespread nervous network, with automatic activity when disconnected from the cord, has been repeatedly discussed by Philip Stöhr Jr.,[108] who believes that the two neuron theory of Langley is incorrect and that the sympathetic nervous system consists of a massive syncytial network of fibers and ganglions. These ganglions not only are present in the cord and in the sympathetic ganglions but are scattered in the periphery. They are capable of regenerating fibers, of automatic function and of reflex activity. Should this revolutionary theory be correct, there is still a marked benefit to be derived from sympathectomy. Central stimuli and spinal reflexes will not affect blood flow. In my experience the saturation of venous oxygen rises permanently, and blood flow is more even, being unaffected by many thermal and emotional stimuli which act through the central nervous system.

In regard to indications for sympathectomy, Pozniakoff and Kohan [109] feel that sweating of the limb is an indication of hypertonus of the sympathetic nervous system and that in a patient affected with Buerger's disease a sweating limb is suitable for sympathectomy whereas a dry one is not. Uprus, Gaylor and Carmichael [110] subjected the test of reflectoric thermal effects to a searching analysis and found that the time of onset of vasodilatation in the limbs of a subject whose blood temperature is not rising rapidly should not be accepted as an indication of a disturbance of a nervous mechanism. They point out that the time of onset of vasodilatation is dependent on local temperature, the posture of the limb and the rapidity of the rise of the temperature of the blood. It seems from this work that the slow rise in the

106. Hirt, A.: Ueber den Aufbau des Spinalganglions und seine Beziehungen zum Sympathicus, Ztschr. f. d. ges. Anat. (Abt. 1) **87**:275 (Sept. 12) 1928.

107. Starlinger, F.: Zum Fernergebnis der Behandlung drohender Gangrän der unteren Gliedmassen durch die Resektion des lumbalen Grenzstranges, Mitt. a. d. Grenzgeb. d. Med. u. Chir. **44**:203, 1936.

108. Stöhr, P., Jr.: Bemerkungen zur Gefässinnervation, Zentralbl. f. Chir. **61**:2 (Jan. 6) 1934.

109. Pozniakoff, L., and Kohan, A.: Examen des réflexes végétatifs dans l'endartérite oblitérante, Rev. de chir. **75**:5, 1937.

110. Uprus, V.; Gaylor, J. B., and Carmichael, E. A.: Vasodilatation and Vasoconstriction in Response to Warming and Cooling the Body: Criticism of Methods, Clin. Sc. **2**:301, 1936.

cutaneous temperature following the application of heat to other parts of the body does not necessarily indicate that vasoconstrictor influences are being overcome.

Leriche and Fontaine [111] reported the result of 1,199 operations on the sympathetic nervous system before the German Surgical Congress of 1936. There were 261 cervical sympathectomies, with 1 death from pneumonia, and 178 lumbar sympathectomies, with 6 deaths, a mortality of 3.3 per cent. Of the 6 deaths, 2 were due to pulmonary embolism and 1 each was due to infection of the wound, streptococcic peritonitis, cerebral hemorrhage and cardiac disease. Studying their indications and results, one must conclude that Leriche is becoming more conservative and that 4 of these deaths occurred in patients who had subacute phlebitis or arteriosclerosis and for whom the operation was not indicated. Leriche states that high lumbar sympathectomy, with removal of the first lumbar ganglion, gives better results than when the second and third ganglions are removed. In regard to sympathectomy versus arterial resection, he feels that resection is more successful in arteriosclerotic patients, whereas sympathectomy gives better results in Buerger's disease. As stated in my previous reviews, arterial resection can have only a limited indication, and its extensive use in arteriosclerotic patients does not seem logical.

In an excellent clinical lecture based mainly on personal observations J. C. White [112] reviews the surgical treatment of the sympathetic nervous system. These procedures are just emerging from the stage of trial and error, partly as the result of an accumulation of clinical evidence but also as the result of a better understanding of the function of these nerves and the development of diagnostic methods. In regard to peripheral vascular diseases, White and Smithwick have performed 18 lumbar sympathectomies for Raynaud's disease, all of which have been successful. The 58 patients who had sympathectomy for the upper extremity, however, have not shown the same amount of improvement. In the first series of 10 cases the upper two thoracic ganglions were removed. This proved to be an inadequate procedure. In the second series the extent was increased to include the inferior cervical ganglion. After early complete vasodilatation there was recurrence of spasms, although the hands remained dry. In the third series of 28 cases preganglionic section was performed by cutting the thoracic chain below the third ganglion and severing the communicant rami to the second and third intercostal nerves. Observations over a period of

111. Leriche, R., and Fontaine, R.: Einige Bemerkungen über 1199 Operationen am Sympathicus, Arch. f. klin. Chir. **186**:338, 1936.

112. White, J. C.: Recent Developments in Surgery of Sympathetic Nervous System, New England J. Med. **216**:91 (Jan. 21) 1937.

one and one-half years indicate that the lasting increase in blood flow in the arm can be as great as that in the leg. In scleroderma and sclerodactylia, in the late stages of poliomyelitis, in hyperhydrosis and in Buerger's disease valuable results have been obtained when the patients have been well selected. The author limits his indications for sympathectomy in Buerger's disease and advises its use for 12 patients in whom crushing of the peripheral nerves has been followed by regeneration and in whom vasospasm again has become a complicating factor.

Telford[28] has now performed lumbar sympathectomy on 112 patients suffering from Buerger's disease. In half the patients the results were good, in one-fourth only fair and in the remaining fourth unsatisfactory. He examined 22 patients who were operated on not less than three years ago in regard to the progress of the disease. Sixteen of the 22 were well, and 6 showed some degree of deterioration. Of these 6, 4 have required low amputation and 2 have had recurrent attacks of phlebitis. Unfortunately no mention is made of the type of postoperative treatment, the removal of foci and other conservative measures. Telford believes that sympathectomy is still the most hopeful of all the treatments that have been advocated.

Sympathectomy would undoubtedly gain more favor among the medical profession if it were performed with strictly limited indications and if the results were carefully followed from year to year. In Raynaud's disease lack of marked structural changes and absence of sclerodactylia have responded favorably; in Buerger's disease one should postulate a definite collateral reserve, absence of acute inflammation or arteriolar destruction and a poor response to conservative treatment. In anterior poliomyelitis moderate paralysis limited to one extremity, evidence of vasospastic phenomena and an age preferably between 6 and 10 years are the indications.[103] Among patients with reflectoric nutritional disturbances, commonly called reflex osseous atrophy, traumatic vessel spasm and traumatic edema, those with severe involvement who are resistant to rest, moderate exercise and physical therapy have done surprisingly well after interruption of the reflex arc by local excision of the irritating focus or by sympathectomy.[84] These reflectoric vascular disturbances need further study and may explain a number of obscure phenomena that have been "dumped into the wastebasket of vegetative neuroses."

AMPUTATION

In spite of the increasing interest in the early conservative treatment of peripheral vascular disease, amputation will always be necessary to relieve intractable pain, to remove a part hopelessly lost and to

restore economic efficiency of the patient. Blencke [113] has studied the late results of 372 amputations which he has performed, mostly on soldiers injured in the World War. His technical advice need not be reviewed here except to state that he does not believe in direct weight bearing and that he reports on a number of late reamputations of seemingly excellent stumps. Crossan [114] believes in a two stage amputation for diabetic gangrene; a simple guillotine amputation is made about 2 handwidths below the tibial tubercle, and a few weeks later secondary closure is made.

The use of a polyvalent serum for gas gangrene is reported by Bates.[115] For a group of 16 patients with gas gangrene treated without serum, the mortality was 50 per cent; for another group of 16 for whom serum was an essential part of the treatment, the mortality was 16 per cent. Bates advocates the preoperative prophylactic use of serum for patients who are to undergo amputation for diabetic or arteriosclerotic gangrene. This, with other prophylactic measures, is undoubtedly decreasing the mortality following amputation throughout the country. It is one of the future tasks of reconstructive surgery to devise suitable effective artificial limbs. No progress has been made in this field for a long time.

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113. Blencke, A.: Unsere Amputierten der letzen 3 Jahre vom Standpunkt des Prothesenbauers betrachtet, Zentralbl. f. Chir. **63**:2299 (Sept. 26) 1936.

114. Crossan, E. T.: Two Stage Amputation for Diabetic Gangrene of Leg, Am. J. Surg. **33**:18, 1936.

115. Bates, M. T.: Gas Gangrene: Review of Thirty-Two Cases with Special Reference to Use of Serum, Both Prophylactic and Therapeutic, Ann. Surg. **105**: 257, 1937.

News and Comment

ACADEMY OF PHYSICAL MEDICINE

The Fifteenth Annual Meeting of the Academy of Physical Medicine will be held at the Hotel Walton, Philadelphia, on Oct. 19, 20 and 21, 1937.

The academy, which is international in scope, will present a scientific program based on reports of the most recent research and practice of the various specialties. In addition to the lectures, demonstration clinics will be held at the hospitals of the University of Pennsylvania, Jefferson Medical College and Temple University.

A copy of the program may be had by addressing the chairman of the Committee on Program and Publication, William D. McFee, M.D., 41 Bay State Road, Boston.

CORRECTION

In the article by Dr. Cecil James Watson, "Studies of Urobilinogen: II. Urobilinogen in the Urine and Feces of Subjects Without Evidence of Disease of the Liver or Biliary Tract," in the February issue (ARCH. INT. MED. **59**:196, 1937), the word "evaluation" was omitted after the word "permit" near the end of the eighth line from the top of page 197.

Book Reviews

Adiposita e Magrezze patologiche: Lavori dei XLII Congressi di medicina interna. By Prof. Francesco Galdi, of Pisa. Pp. 288. Rome: Luigi Pozzi, 1936.

This two hundred and eighty-eight page work is a laborious study of seventeen obese and ten underweight patients. The diagnostic categories into which the conditions noted were placed included Fröhlich's syndrome, diencephalohypophysial obesity, thyroid obesity, essential obesity, essential thinness, thyroid thinness (hyperthyroidism) and Simmonds' disease. Estimations were made of the basal metabolic rate, respiratory quotient, specific dynamic action of several test meals, dextrose tolerance, lipoid tolerance, salt and water metabolism, effect of work on the respiratory quotient and hyperglycemia and effect of insulin, epinephrine and various hormone preparations. Unfortunately no comparative values for normal controls are given, and frequently the method employed is not named. Among the data are several curious values, for instance, values for the respiratory quotient of 1.03 and 0.63. The data for specific dynamic action and the effect of various drugs are irregular.

The conclusions are that the metabolic discrepancies responsible for obesity are either secondary to neuro-endocrine disturbances or autochthonous, i. e. (in the adipose tissue). Essential obesity has a constitutional or predispositional etiology. Exogenous obesity is unusual; rather there is noted an increased avidity of the adipose tissues for deposition of fat. In general this disturbance is thought to originate in the diencephalohypophysial region. The observed alterations of metabolism are secondary to the aforementioned influences. The lipogenous tendency of Bergmann is proved. On the other hand, the author states that the chief cause of pathologic thinness is anorexia, which may be psychic; but in Simmond's disease, exophthalmic goiter and other conditions it is secondary to a disturbance of the diencephalohypophysial region, or it may represent a vegetative neurosis.

On the basis of his studies the author recommends a low caloric-high protein (to increase the specific dynamic action) diet for the treatment of obesity. For the pathologically thin person a high carbohydrate diet, insulin and psychotherapy are indicated. The review of previous work on fat and thin patients is comprehensive, and the bibliography includes about six hundred titles.

Handbook of Orthopaedic Surgery. By Alfred R. Shands Jr., M.D., Associate Professor of Surgery, in collaboration with Richard B. Raney, M.D., Instructor in Orthopaedic Surgery, Duke University School of Medicine. Price, $5. Pp. 593, with 169 illustrations. St. Louis: C. V. Mosby Company, 1937.

This is a book to delight the heart of those who are trying to learn medicine or who are struggling with the medical curriculum, for it lays out in a sensible manner a sensible course in orthopedic surgery.

In 1934 the Committee on Undergraduate Instruction in Orthopaedic Surgery of the American Orthopaedic Association called attention to the fact that in several of the leading medical schools approximately twenty-four class periods each of an hour's duration are profitably employed for undergraduate instruction in this special subject. The authors of this handbook have assembled a twenty-four chapter book. All of the chapters are of approximately the same length. In the various chapters are discussed the subjects that might go to form the skeleton for a useful teaching course in orthopedic surgery; and, what is more, the manuscript of each of these chapters received due criticism by one or more competent reviewers before it went to press.

While in a sense the volume was written by many authors, yet in reality, having been put together by one, or at the most two, authors, it has a comfortingly uniform style throughout, and the story is continuous. The illustrations are clear and in large measure from the facile pen of Mr. Jack B. Wilson, whose original manner of medical illustrating is now so familiar. And last but not least, at the end of the book, in addition to a good index, there is a separate bibliography for each of the twenty-four chapters, giving references up to January 1937.

It goes without saying that this handbook will prove extremely useful. As an interested teacher, this reviewer inquires: Would it be possible in the next edition to devise some loose-leaf plan by which between new editions both text and references can be kept perpetually young and up to date.

La cianosis de los cardiacos negros de Ayerza: Su estudio semiológico, clínico y fisiopatológica. By Eduardo L. Capdehourat, M.D. Pp. 372. Buenos Aires, Argentine: Aniceto Lopez, 1934.

This monograph, consisting of eight chapters and sixteen case reports, is devoted to a broad consideration of the clinical entities in which cyanosis, pulmonary fibrosis, emphysema and failure of the right side of the heart, with or without sclerosis of the pulmonary artery, are manifested. The author gives syphilis little part in the pathogenesis of these states and blames chiefly chronic injury due to infections of the respiratory tract and noxious physical agents, such as dust and gases. It is clear that in Buenos Aires Ayerza's syndrome is considered much less an etiologic entity than a condition due to pathologic physiology. North American physicians are still puzzled over the apparently high incidence of "cor pulmone" in South America. The especial objective of the dissertation is the presentation of data and discussions on pathologic physiology of cyanosis, and this is achieved in splendid fashion. The clinical observations and physiologic measurements, including studies of pulmonary ventilation, cardiac output and chemical constituents of the blood, comprise a valuable contribution to the medical literature.

Treatment of Diabetes Mellitus. By Elliott P. Joslin, M.D., M.A. Price, $7. Pp. 707. Philadelphia: Lea & Febiger, 1937.

An extended comment on the book which is the vade-mecum in the literature on diabetes hardly seems necessary, particularly as this is the sixth edition of what may truly be called a standard textbook and book of reference.

The introduction of "protamine insulin necessitates the revision of this book." The data that have been studied to convince Joslin and his associates consist of reports of over twelve hundred cases in which this new insulin preparation has been administered. Joslin is enthusiastic about protamine insulin. He acknowledges that some patients experience difficulty in becoming adjusted to the new drug, but these instances are few and far between. As a matter of fact, only ten of the total number of patients had any difficulty. The ages of these patients varied from 7 to 62 years, and the reasons for the difficulties were many.

The remainder of the book adheres closely to the subject matter as presented in previous editions.

Röntgenatlas der Erkrankungen des Herzens und der Gefässe. By Dr. W. Brednow, Privatdozent for Internal Medicine and Roentgenology and Chief Physician of the University Medical Clinic, Göttingen. Price, 10.50 marks. Pp. 155, with 87 illustrations. Berlin: Urban & Schwarzenberg, 1936.

This is a textbook for cardiologists setting forth the roentgen evidence elicited in examination of the heart and blood vessels. Numerous models have been photographed to illustrate the various points brought out in the roentgenograms. The illustrations are exceptionally clear, and the halftone reproductions of both photographs and roentgenograms are beautifully made. The brief text is distributed, page by page, throughout the work, facing the illustrations. This is an excellent book and should be valuable for any physician utilizing roentgen aid in cardiovascular diseases.

Registro e interpretacion de la actividad cardiaca. By Oscar Orias, M.D. Pp. 193, with 77 illustrations. Second edition. Buenos Aires, Argentine: El Ateneo, 1936.

This monograph describes clearly the possibilities for physiologic observation of cardiac and vascular phenomena by means of graphic methods, chiefly the optical manometers of Wiggers. The reviewer is greatly impressed with the perfection of the records used as illustrations.